Chem Ed

EDITORIALLY SPEAKING

EDITOR'S NOTE. The essay that follows was written several years ago by a then unknown chemist who at the age of 29 was completing his fourth year of teaching at a small college. It is based on the last part of a talk presented at the student science club on "Some Experiences in Research," in which the speaker reviewed experimental work he had done while guiding his first group of students from freshman year to the point of graduation. Starting with no brilliant new ideas, he says, but rather by making obvious extensions of the theme of his work for the doctorate, he had found plenty to keep him occupied and to relate to the student group. He now feels that the concluding remarks may be of some interest but that they should stand on their own merit without identification.

An Anonymous Commentary on Research

This account of my experiences may make you feel, as I do, that the work of an investigator is an exceedingly thrilling and fascinating game. It will show you also that an exceptional intelligence is not required, for one can make a wholly unoriginal start and soon find himself running into new ideas and problems and experiencing romantic adventures of discovery. But obviously a person must have a love for the subject so great that he is prepared to work very hard and to make any sacrifice needed.

One further quality which the scientific worker should possess occurred to me while witnessing a wrestling match. These wrestlers gave everything they had, and then came back with more. Special finishing holds are designed to pin the other fellow's shoulders to the mat, but it is impossible to clamp a finishing hold onto two hundred thirty pounds of muscle and skill without an argument. The only chance is to weaken your man, catch him off guard for an instant, and then apply one of these holds. Most of the battle involves trying to weaken your man with terrifying punishing holds.

My companion pointed out that wrestlers and fighters as a class have been found to be much less sensitive to pain than the average man. They are qualified for the calling because they can stand the punishment. They know what it is; they come back for more.

Should not the scientist also be one who can take punishment? Mental agony surely is no less severe than physical. Halfway through a seemingly sound attack on a problem, you may find that you have run into a stone wall; that what you wanted so much to accomplish is either impossible or beyond your power. It is thrilling to do battle against the unknown, but baffling to feel that you are hurling yourself against the unknowable. Even a minor failure, when not tempered with an understanding of the reason for the failure, is a very real form of punishment which the scientist must be willing to face.

As an example of a minor failure, I shall tell you about the last ten analyses I have made. A combustion analysis of a new compound is not very difficult, but it takes two or three hours, uses up some of the valuable sample, usually the world's supply at the time, and involves a certain nervous tension. It is thus a considerable relief to mark O.K. after the result and perhaps to carve a notch in the shelf to record the acquisition of another new compound.

But the last ten of my analyses bear the notation N.G. I analyzed three compounds repeatedly with all the care I can command, but the results are all unsatisfactory. That the results do not agree with my formulas for the compounds may mean that the analyses are faulty, that the formulas are wrong, or that the compounds are impure. I have confidence in the analyses, the formulas seem to be correct, and I feel sure that the compounds are pure. But I cannot publish such results, and the situation is most unpleasant. I wanted to send off a paper to a German journal in a hurry but had held it pending satisfactory analysis of two compounds. Well, I decided the other day to take a licking on these two compounds. I have no idea of what is wrong or of where to turn, and the best thing I can do is to admit that I am beaten and take the punishment.

Such an experience is certainly annoying, and yet I am not discouraged or deeply bothered by the failure. The man who has the proper temperament and who can come back for more may be rewarded in the end. I tried four times to synthesize a compound, but each of the four methods failed. I finally established the structure by conversion to another compound, and synthesis of the latter brought with it as a by-product the discovery of a new reaction.

I feel free to mention these experiences because a scientist deserves no more praise for his attitude than does the wrestler for his insensitivity to pain; some are built that way; some are not. And difficulties only

make the game the more fascinating. When the way to an end must be fought out over many obstacles, attainment of the goal brings an added satisfaction. The compound mentioned above was derived from another which I had isolated from a complicated reaction mixture only on the second attempt, and after carrying out fractional crystallizations over a period of three months. I collected 0.7 g of the substance; it was new, and for the completion of the problem I needed to establish the structure. I used 0.1 g for an analysis, which came out satisfactorily. A further 0.2 g was used to prepare one derivative, and 0.2 g for another. The results established the empirical formula, but the positions of the hydroxyl groups remained in doubt. With 0.2 g left I tried, with much trembling, a reaction which usually yields only 30–40% of the theoretical amount. In this case the oxidation happened to go nearly quantitatively and afforded enough material for an analysis. I first tried a color test, and very fortunately a positive result revealed the structure of the compound; that is, if the analysis were to be confirmatory. For this analysis I used the last 0.1 g of sample, and it was nervous business. I had a happy inspiration and waited until Christmas morning when, sure enough, I had a Christmas present in the form of a good analysis and completion of the problem.

Addendum

The description of my distress over the faulty analyses must have been more graphic than I can bring myself to record in this written account, for I was embarrassed for two or three days after the talk by profound expressions of sympathy on all sides. For one of the compounds, which formed excellent crystals, the faulty analyses were as follows. Calc'd.: C, 85.69; H, 4.38. Found: C, 83.90, 84.50, 84.72; H, 4.38, 4.43, 4.41. I had tried the Dennstedt contact star, the Haas cuprous chloride method, fast and slow combustions, and a mixture with lead chromate, without any improvement. Following the discussions after my talk, I finally remembered the experience of S. C. Hooker, who had earned the Ph.D. degree at Munich after one year of research by devising a method for the satisfactory analysis of retene derivatives. I then tried his technique of using a tube packed with nothing but lead chromate and heated to a red glow. Analysis of the compound mentioned, by this method, gave the results: C. 85.70; H, 4.51. The other two compounds were analyzed successfully by the same procedure.

* * *

Condensed Norms: ACS Cooperative Examinations

BIOCHEMISTRY FORM 1959

Maximum possible score	One semester[a] group 135	Two semester[b] group 135
Percentile rank		
99	90.0	103.5
95	70.0	95.5
90	58.8	85.5
85	50.5	79.5
80	45.3	74.7
75	42.0	72.0
70	38.3	67.7
65	36.0	64.7
60	33.4	62.0
55	31.5	59.0
50	30.5	57.2
45	29.3	54.8
40	28.5	52.8
35	27.9	50.0
30	26.9	48.0
25	24.7	44.9
20	21.8	41.1
15	20.5	38.1
10	17.5	34.3
5	15.0	30.2
1	7.0	21.8

The scoring formula used was R-W/4 throughout.
The figures given are raw scores.

[a] The norms for the One Semester Group are based on scores of 110 students from 4 institutions. The students received from 2 to 4 hours credit, with a mean of 3.8; lecture time varied from 2 to 3 hours per week with a mean of 2.9; and laboratory time per week ranged from 2 to 3 hours with a mean of 2.8.

[b] The norms for the Two Semester Group are based on scores of 392 students from 7 institutions. The students received from 3 to 5 hours credit, with a mean of 3.8; lecture time varied from 2 to 5 hours per week with a mean of 3.4; and laboratory time per week ranged from 0 to 6 hours with a mean of 2.9.

HIGH SCHOOL CHEMISTRY TEST FORM N

Maximum possible score	Sub groups A[a] 90	B[b] 90	C[c] 90	D[d] 90	Entire group[e] 90
Percentile rank					
99	81.0	80.7	74.3	83.6	81.0
95	66.0	71.2	63.5	76.2	72.2
90	59.3	64.8	56.8	72.5	64.0
85	55.7	60.2	53.0	68.1	58.7
80	48.5	56.0	49.8	64.2	54.4
75	43.6	52.0	47.0	60.9	51.0
70	39.5	49.3	44.4	58.2	48.3
65	37.5	46.6	41.6	56.1	45.2
60	34.3	44.1	39.5	53.5	42.7
55	31.8	41.6	38.0	50.7	40.0
50	29.4	39.3	36.5	48.8	37.7
45	27.3	37.2	34.5	46.5	35.1
40	24.7	34.8	32.3	43.8	32.9
35	22.6	32.3	30.7	40.6	30.4
30	20.6	29.5	28.7	38.3	27.8
25	18.7	26.8	26.1	35.4	25.2
20	16.2	24.5	24.0	32.7	22.7
15	13.7	21.3	21.8	30.0	19.7
10	11.5	17.7	18.9	25.9	16.5
5	8.2	13.0	13.5	19.8	11.8
1	4.7	6.2	8.7	11.3	5.2

The scoring formula used was R-W/4 throughout.
The figures given are raw scores.

[a] Sub Group A consists of sophomores, juniors, and seniors with no previous course in physics and having 0–2 semesters of mathematics prior to taking the chemistry course.

[b] Sub Group B consists of juniors with no previous course in physics and having 4–6 semesters of mathematics prior to taking the chemistry course.

[c] Sub Group C consists of seniors with no previous course in physics and having 6–8 semesters of mathematics prior to taking the chemistry course.

[d] Sub Group D consists of seniors having had 2 semesters of physics and 6–8 semesters of mathematics prior to taking the chemistry course.

[e] Entire Group is a random sample of all students reported.

Condensed Norms: ACS Cooperative Examinations

Two new tests were released in the spring of 1959, High School Form 1959 and Biochemistry Form 1959.[1] The norms on these tests have been calculated from the reports, and a condensed version is given below. In addition new norms have been calculated for the High School Form N.

The condensed norms are selected from a much larger body of data which can be obtained from the Examinations Committee, American Chemical Society, Theo. A. Ashford, Chairman, 1402 South Grand Boulevard, St. Louis 4, Missouri.

Reviews

Biochemistry, Form 1959

The Cooperative Examination in Biochemistry constitutes a part of the testing program of the ACS Division of Chemical Education. The latest revision of the test, Form 1959, consists of 135 multiple choice questions divided into two parts, the first with 75 items and the second having 60 items. Fifty minutes is allotted for each section.

As stated in the instructions to the Examiner, Part I is "elementary in character and designed for one-quarter or one-semester survey courses in Biochemistry, and Part II being more advanced and suitable (together with Part I) for intensive one-semester, two-quarter or one-year courses." Qualitatively, the two parts are very similar in the material covered and whether Part II really deserves the title of "advanced" might be questioned.

Obviously, the task of sampling a student's comprehension of modern biochemistry with 135 questions represents a formidable challenge, and the examination committee has done a commendable job in trying to achieve a proper balance in the material covered by the test. However, in the reviewer's opinion, too great a proportion of the questions involves memory, and not enough emphasis is placed on broader aspects of molecular biology. To cite a few examples, topics such as the following receive little or no attention: current concepts of macromolecular structure (protein and DNA); principles of oxidation-reduction and the general role of dehydrogenation in biological systems; the role of equilibria and free energy changes in biochemical reactions; mechanisms of enzyme action; the catalytic nature of the citric acid cycle in energy production and the integrative functions of these reactions in the metabolism of carbohydrate, fat, and amino acids; etc. With such omissions it would be of interest to know whether the pattern of questions in the examination reflects the content of our present courses in elementary biochemistry. If it does, there might be cause for asking whether these courses need revision and also whether they have assumed their rightful relation to other chemistry and biology courses in undergraduate curricula. Such an inventory is long overdue under any circumstances.

Regardless of the omission of certain topics, the 1959 edition of the Biochemistry Examination is a worthy contribution to the testing program of the Division of Chemical Education and should prove very helpful in the task of student counseling.

WILHELM R. FRISELL
University of Colorado School of Medicine, Denver

High School, Form 1959

The 1959 ACS—NSTA Cooperative Examination for High School Chemistry is well planned and includes all important concepts developed in the first year. Objective exercises include recall of information, application of principles, and quantitative application of principles. An examinations subcommittee composed of outstanding secondary school teachers carefully screens, edits, and pretests each item. The test is designed to determine pupil achievement as compared with established norms. Subject matter covered indicates what the committee considers fundamental to a good high school course.

The questions, all multiple choice, are free from the ambiguity which often plagues the student when this type of question is used. A well-prepared class will not find the test so difficult as to be frustrating and discouraging.

It is deplorable that many high schools have eliminated midyear and final examinations. Retention is short-lived without frequent review, and often the logical development which makes science courses stimulating and interesting is missed when the student is not required to organize and review large areas of material.

This examination is a reliable objective measure of pupil mastery of concepts and skills and an effective summation of the year's work.

CHRISTINE JANSING
J. M. Atherton High School
Louisvillle, Kentucky

HIGH SCHOOL CHEMISTRY TEST FORM 1959

Maximum possible score	Sub groups A[a] 100	B[b] 100	C[c] 100	D[d] 100	Entire group[e] 100
Percentile rank					
99	89.5	91.4	84.5	93.2	91.9
95	75.3	80.9	75.5	86.0	80.4
90	63.5	73.0	67.5	80.6	72.4
85	52.3	67.0	62.1	76.0	65.8
80	44.7	61.6	56.0	72.0	60.4
75	38.9	57.5	52.0	68.5	56.0
70	34.6	53.6	49.1	65.0	51.1
65	31.1	49.5	46.5	61.3	47.3
60	28.2	46.3	44.4	58.4	43.8
55	26.0	43.5	41.0	55.0	40.8
50	23.8	40.7	38.3	51.4	38.5
45	20.7	38.0	35.8	48.1	35.6
40	18.8	34.9	34.0	44.6	33.1
35	16.8	32.2	31.0	41.5	30.1
30	14.4	29.4	28.0	38.1	27.3
25	12.0	26.5	24.8	35.2	24.5
20	8.6	23.6	21.7	32.4	21.5
15	6.7	19.8	18.7	28.9	18.0
10	4.7	16.0	14.9	25.1	13.5
5	2.6	11.2	10.6	17.5	8.7
1	0.2	4.0	1.0	7.0	3.2

The scoring formula used was R-W/4 throughout.
The figures given are raw scores.

[1] Condensed norms for the currently used ACS Cooperative Examinations have appeared in THIS JOURNAL, **34**, 144 (1957); **35**, 244 (1958); and **36**, 148 (1959).

A Chem Ed SYMPOSIUM

50th Anniversary / Division of Medicinal Chemistry

The birth of the Division of Medicinal Chemistry was heralded in the advance announcements of the Meeting of the American Chemical Society held in Baltimore on December 27, 1908 to January 1, 1909, which stated, in part, that Professor Edward Kremers of the University of Wisconsin had accepted the responsibility for a program in pharmaceutical chemistry.[1] Included in the minutes of that meeting is the following:[2]

> After careful consideration it was further voted that a committee of three be appointed by the President to consult with the pharmaceutical chemists of the Society as to the advisability of recommending the formation of a Division of Pharmaceutical Chemistry to the Council.

President Whitney appointed to the committee Professor Kremers; Professor A. B. Stevens of the University of Michigan, who was elected temporary chairman; and Dr. R. L. Murray, of Merck and Company, who served as temporary secretary. These three arranged for the first official program for the Division, held at Detroit, June 29 to July 2, 1909. Concerning the first business session of the proposed Division, we read:

> The first business taken up was a discussion of the advisability of requesting the Council to establish a Division of Pharmaceutical Chemistry. The meeting was decidedly enthusiastic and thirty-five listed themselves on the roll call—it was unanimously voted to recommend to the Council that a Division of Pharmaceutical Chemistry be formed.

In anticipation of approval by the Council the duly elected officers were: chairman, A. B. Stevens; secretary, B. L. Murray; executive committee, Edward Kremers, J. P. Remington, and J. M. Francis. By letter ballot sent out on October 12, 1909, the Council unanimously approved the organization of the Division.

The objectives were outlined by the first secretary in the following words.[3]

> And it will be an excellent beginning for this New Division of Pharmaceutical Chemistry to investigate and, if possible, to agree upon some or a few methods of analysis now entirely omitted from and so much needed in the United States Pharmacopoeia.

This is entirely understandable, for on June 30, 1906, the first Food and Drug law went into effect, and the *U. S. Pharmacopoeia* was now empowered to set up legal standards for quality and potency of drugs; many new reliable methods of assay were needed.

However, in a fast-moving world of science, change is *de rigueur*, and the first objectives had to be amplified and finally seem even to have been forgotten.

With the advent of World War I synthetic drugs which had established a place for themselves in this country could not be imported, and American scientists were called on to supply the deficiency, e.g., local anesthetics, barbiturates etc., thus bringing on the scene names like Dox, Shonle, Volwiler, and many others. Not only were the deficiencies taken care of, but newer and more efficacious remedies began to make their appearance. In harmony with the newer trends, the By-Laws of the Division were changed in 1927 and reaffirmed in 1938 to read:

> Article I. *Name and Object*
>
> Section 1. This Division shall be known as the Division of Medicinal Chemistry of the American Chemical Society.
>
> Section 2. The objective of this Division shall be the advancement of knowledge of chemistry and pharmacology of substances used in medicine.

It is to be expected that the members of the Division are alert to new challenges, and already many papers appear on the Division's programs which describe the pathways by which drugs are metabolized or detoxified; that is, the reactions or mechanisms by which chemical agents produce their desired therapeutic effects. Our chemists are more and more cooperating with the biologists to attain "completely new horizons—that justify the hope of achieving one of their ultimate aims, namely, to understand the living cell on a molecular level in terms of physics and chemistry."[4]

Walter H. Hartung, *presiding*
Medical College of Virginia, Richmond

The cover

The CIBA laboratory pictured on the left was operating in France when the half-century spanned by this symposium began. The photograph on the right shows a present-day laboratory tool, a Craig counter-current distribution apparatus for fractionation and purity studies on natural products in the Merck organic and biochemical research department. These photographs were selected from those made available by CIBA through the courtesy of Dr. Albert J. Plummer, Director of Macrobiology, and Mr. Gaylord J. Haftiezer of the public relations division and from Merck Sharp & Dohme by Dr. Max Tishler, President, and Miss Janet King of the public relations department.

The Editor is grateful to many who have made the publication of this symposium possible. Dr. John H. Biel, Secretary of the Division of Medicinal Chemistry, deserves much of the credit for assembling the manuscripts. The illustrative photographs scattered throughout the text were made available by Dr. Edward Elslager of Parke Davis Co.

[1] *Ind. Eng. Chem.* **1**, 53 (1909).
[2] *J. Am. Chem. Soc.* **31**, proceedings p. 31 (1909).
[3] *Ind. Eng. Chem.* **1**, 776 (1909).
[4] NACHMANSOHN, D. A., *Annals of N. Y. Acad. Sci.*, **81**, 219 (1959).

John C. Krantz, Jr.
University of Maryland
School of Medicine
Baltimore, Maryland

Volatile Anesthetics and Analgesics

Pain is the arch enemy of mankind. To escape its ravages, to achieve a surcease from its devastating blows, man has ransacked the entire world to obtain drugs that would obtund pain. This has been a universal quest of mankind, for pain is a tax that is levied on everyone for the privilege of life on this planet. Some are taxed lightly, others are taxed heavily, but all are taxed. In "Paradise Lost" Milton declared, "Pain is perfect misery, the worst of evils, and excessive, overturns all patience."

Physiologically, pain is a specific sensory experience which is mediated through nerve structures which are separate from those which mediate other sensations, such as touch, pressure, heat, and cold. Pain is recognized as a warning signal of danger to the organism. Since the awareness of pain is dependent upon consciousness, it follows that the obliteration of consciousness will cause the complete abolition of pain. Through a long history of the use of opium, mandragora, and alcohol to quell the pain of surgical trauma, man discovered the use of the volatile anesthetics during the decade 1840–50. The names of Horace Wells, William T. G. Morton, Crawford W. Long, and James Y. Simpson are associated with this illustrious chapter in medical history. Until the turn of the century, the three anesthetics, nitrous oxide, ether, and chloroform were the principal agents in the physician's armamentarium employed to produce surgical anesthesia. General anesthetics abolish the perception of nerve stimuli, produce a hiatus in consciousness, and obliterate motor activity. No class of drugs has contributed more to human welfare than the anesthetics. They have made modern surgery possible, and changed the operating room from a chamber of horrors to a place where the tranquility of unconsciousness supervenes.

Mechanism of Anesthetic Action

That the living cell can become the site of consciousness is perhaps the most baffling and yet intriguing problem in biology. An equally difficult and puzzling problem is the mechanism of action by which chemical compounds such as the volatile anesthetics, not metabolized by brain cells, can produce a hiatus in consciousness. Lillie stated the problem so cogently many years ago, "The problem of general anesthesia is a fact inseparable from the wider problem of the nature and conditions of irritability in general."

The first major assault in the problem dates back to the turn of the century when Hans Horst Meyer and E. Overton expressed a theory of narcosis in the following postulates:

1. All chemically indifferent substances which are soluble in fats and fatlike bodies must exert a narcotic action on living protoplasm, insofar as they can be distributed in it.
2. The effect must manifest itself first, and most markedly, in those cells in which fatty or lipoid substances predominate in the chemical structure and presumably in which they form essential participants in the cell function; viz., in nerve cells.
3. The relative efficiency of such narcotic agents must be dependent upon their mechanical affinity for lipoid substances on one hand, and for the remaining body constituents, i.e., principally water, on the other hand. Their efficiency is therefore dependent upon their partition coefficient which determines their distribution in a mixture of water and lipoid substances.

One is inclined to call these time-honored postulates a statement of narcotic distribution in the body rather than a theory of narcosis. However, when viewed with respect to our present knowledge of cellular respiration they represent a definite contribution which has withstood the pruning knife of time.

Our experience with the oil/water coefficients of newer anesthetic agents has been most gratifying. In general, we observed that the oil/water coefficients of many of the commonly used volatile anesthetics, could be plotted against the reciprocal of their water solubility. The latter physical constant is most readily measured and enables one to make a first approximation of the potency of an anesthetic agent (*1*).

Since anesthetic potency and oil/water coefficients vary with each other, and the oil/water coefficient varies with the insolubility in water, it follows that potency and the reciprocal of water solubility bear a direct relationship to each other (*1*).

The formulas of three generally used anesthetics namely nitrous oxide, ethyl ether, and cyclopropane show a wide variation in chemical constitution. One property in common, however, is a high oil/water coefficient. Some ten years ago we prepared cyclobutane and studied it pharmacologically and clinically as an anesthetic agent. Its properties were strikingly similar to those of cyclopropane. However, owing to the greater difficulty in synthesis the use of cyclobutane was abandoned. Cyclopentane, the next member in the series, which is inexpensive and enjoys a high oil/water coefficient elicited unconsciousness in dogs and monkeys with marked clonic convulsive seizures. Thus it appears that, although these volatile anesthetic agents enter and leave the brain unchanged, the cells of the brain are exquisitely sensitive to their chemical configurations.

Presented as part of the 50th Anniversary Symposium, Division of Medicinal Chemistry, American Chemical Society, September 16, 1959, Atlantic City, New Jersey.

Ferguson (*2*), in considering an interpretation of his data on the action of volatile anesthetic agents, pointed out that solubility, vapor pressure, oil/water coefficients, and adsorbability, were measures of the tendency of the agents to distribute between two phases. Further when equilibrium was established, the chemical potential would be the same in both phases. Brink and Posternak (*3*) contend that the work required in the transfer from the pure liquid to the narcotized cell is the same for all substances which produce equal degrees of narcosis at equal thermodynamic activities. They speculate that anesthetics probably produce their effect in the regions of the cell in which their molecules fit much as they fit into their own pure liquid phase. Wulf and Featherstone (*4*) consider these concepts consistent with their hypothesis, namely, that the increasing potency of clinical anesthetic agents parallels in general the van der Waals' constants. Based upon these data they were able to account for the anesthetic action of the inert gas Xenon. They point out that its anesthetic potency should be equivalent to that of nitrous oxide and ethylene, since the van der Waals' constants are essentially the same. And it is true that Xenon, nitrous oxide, and ethylene do exhibit about the same degree of anesthetic potency.

These interesting studies of the physical properties of anesthetic agents have contributed much useful information to our knowledge. But the key to the problem lies in an understanding of what distortion of enzymic activity is provoked by their presence in the brain, which in turn is responsible for the hiatus in consciousness.

Many studies have been designed to pinpoint the specific enzyme system which is responsible for anesthetic action and the concomitant loss of consciousness. Numerous anesthetic agents have been shown to depress the oxygen uptake of brain brei. They exert little or no effect upon anaerobic glycolysis. It appears that in the process of the main line oxidation, anesthetics interfere with a sensitive flavoprotein which connects the phosphonucleotide dehydrogenase system with the cytochromes. The depression is reversible.

It has been shown that there are many ways in which an anesthetic agent can exert its effect upon cerebral enzyme systems and evoke unconsciousness. Furthermore, all of the generally used anesthetic agents do not achieve anesthesia by affecting the same target enzyme system. For example, Brody and Bain (*5*) demonstrated that barbiturates in anesthetic concentrations uncoupled oxidation from phosphorylation in the mitochondrial fraction of the rat's brains. Hulme and Krantz (*6*) showed that diethyl ether produced a similar type of uncoupling of oxidation from phosphorylation.

Since the high energy phosphate bonds of adenosine triphosphate are necessary for the synthesis of acetylcholine, a diminution of the level of ATP would result in a paucity of acetylcholine essential for neuronal transmission. However, Xenon which may be classed as a volatile anesthetic, was shown by Featherstone and Levy (*7*) to be incapable of uncoupling oxidation from phosphorylation. Nitrous oxide likewise does not affect this enzyme system. Nevertheless, Hosein, *et al.* (*8*) demonstrated that nitrous oxide inhibits anaerobic glycolysis and also depresses certain facets of the hydrogen transport system.

Implicit in these statements is the fact that the precise mechanism of anesthesia at an enzyme level has not been delineated. The enzymic activities responsible for consciousness appear to be so complex and intricately interdependent that an agent influencing one segment of the system concomitantly affects the harmonious function of the whole. In addition it seems likely that the anesthetic agents in use affect the enzymic activity of the brain at different links in the complex chain of consciousness.

In summary, it appears that our present knowledge permits the following generalizations:

1. The use of the Overton-Meyer theory as a statement of anesthetic distribution in the body.
2. The presence of the agent in the central nervous system attacks the "main line" oxidation in the cells of the central nervous system. The target enzymes for different anesthetics are not always the same.
3. Anesthetics have been shown to act on a flavoprotein connecting the phosphonucleotide dehydrogenases with the cytochromes. Certain agents uncouple oxidation from phosphorylation.
4. The enzymic inhibitions are reversible processes.

Fluorine-Bearing Anesthetic Agents

Halogen-bearing anesthetic agents have occupied an important place in the armamentarium of the anesthesiologist for many years. Thus chloroform and ethyl chloride were among the first volatile anesthetics employed. Tribromoethanol also has been extensively used. Within the last two decades the synthesis of many fluorinated hydrocarbons and ethers has prompted their use as anesthetic agents. Robbins (*9*) studied a large number of fluorinated and mixed halogenated hydrocarbons on animals; not any of these appeared to be suitable for human anesthesia. Lu, Ling, and Krantz (*10*) extended these studies and found trifluoroethyl vinyl ether (Fluoromar) suitable for anesthesia in man. This appears to be the first fluorinated volatile anesthetic to have been used on man and made available for clinical anesthesia. This was followed by the clinical application of 1,1,1-trifluoro-2,2-bromo-chlorethane (Fluothane) by Raventos (*11*). In our further studies with fluorinated ethers, it was observed that hexafluorodiethyl ether (Indoklon) elicited violet convulsive seizures upon inhalation. This prompted us to use the agent in the treatment of mental illness as a substitute for electroshock therapy (Krantz, Truitt, and Kurland) (*12*). Many thousands of such treatments have been given with gratifying results. Of more than passing interest is the observation that Indoklon, a convulsive ether, enjoys little oil solubility, whereas Fluoromar, an anesthetic ether has a high oil/water coefficient.

Thus advances in the practical application of the volatile anesthetics have been marked; indeed they have far outrun our theoretical concepts of their mechanism of action.

The Non-Narcotic Analgesics

The anesthetics obtund pain by the abolition of consciousness. The narcotic analgesics relieve pain by increasing the threshold to pain and diminishing the alarm reaction to recurring pain. This is frequently accompanied with altered mental alacrity and the hazard of addiction. The non-narcotic analgesics obtund pain without interference with mental acuity and present no addictive hazard.

The final stage of testing drugs at the Sloan-Kettering Institute is their use in treating cancer patients.

The non-narcotic analgesics are usually not effective in the relief of deep-seated visceral pain. They are not efficacious in affording relief from excruciating, sharp, and intense pain. However, they find a wide field of usefulness and are most valuable in the relief of arthralgias, myalgias, neuralgias, cephalalgias, and integumental pain in general.

Although the mechanism of action of the commonly used non-narcotic analgesics has not been conclusively delineated, certain evidence points to a tentative hypothesis for their use as analgesic drugs. Since these drugs do not interfere with the cortical activity of the brain by interference with mental alacrity, it is likely that their action is mediated at a subcortical level. They appear to interfere with pain impulses carried over the lateral spinothalamic tract, raising the threshold of stimuli relayed from the thalamus to the sensory areas of the cerebral cortex. With the relief of pain mediated through the action of morphine or other narcotic analgesics, the tranquilizing of the patient and the suppression of the alarm reaction often persists longer than the increase of the threshold to pain. With this type of analgesia a second noxious stimulus reaching the sensorium is acutely recognized. With analgesia produced by the non-narcotic analgesics, additional noxious stimuli are not perceived owing to the blockade of the pain pathway below the sensorium.

The first and now most generally used agents in the class of non-narcotic analgesics are the salicylates and their derivatives. Salicylic acid was isolated from salicin by Piria in 1838. Sodium salicylate was used in medicine for the first time by Buss in 1875. Augmenting sodium salicylate in the field of analgesia in the decade 1880–90 came acetanilid, acetophenetidin, and antipyrine. At the turn of the century Dreser synthesized acetylsalicylic acid which was called aspirin from the German word "Spirsaure" which is the German word for salicylic acid.

That aspirin occupies a place of pre-eminence in the field of non-narcotic analgesics is evidenced by the fact that the American public consumes it, in its various dosage forms, to the extent of 21 tons daily. In addition to the use of low dosage levels of aspirin for headaches and minor neuralgic pain, aspirin does not suffer in comparison with ACTH and corticosteroid therapy in rheumatic fever and the various arthritides. Besides its analgesic and antipyretic actions, Reid (*13*) demonstrated that salicylates served as a primary metabolic stimulant (*13*). The pulmonary ventilation increase which is elicited by large doses of salicylates appears to be a response to the demand for a greater utilization of oxygen in the periphery. It is possible that the antirheumatic action of aspirin is associated with its peripheral metabolic stimulating action.

New additions to this class of analgesics have been few. The well-established mixtures of aspirin, phenacetin, and caffeine, APC, are abundantly used and within their field of usefulness appear to be effective. Salicylamide does not offer any advantage over aspirin. Furthermore it has not been established that acetopara aminophenol (APAP) is superior to acetophenetin. Undoubtedly the most dependable and potent of the non-narcotic analgesics is aminopyrine. Unfortunately this compound has been incriminated in the production of blood dyscrasias and its indiscriminate sale in this country is prohibited. However, this condition does not prevail in many countries in Europe and aminopyrine is extensively used for the relief of pain. It appears to this observer that the evidence against the use of this potent analgesic should be re-investigated and its validity assessed by further controlled clinical studies.

More recent additions to the non-narcotic analgesics are Darvon (Lilly) and Zactirin (Wyatt). Darvon is α,α-4-dimethyl-amino-1,2-diphenyl-3 methyl 1-2-butanol proprionate hydrochloride and Zactirin is ethoheptazine citrate. Each drug has a wide margin of safety and offers no addictive hazard. Reports from various sources are somewhat conflicting regarding the analgesic action of each of these drugs. However, reports indicate that Darvon is as potent as codeine as an analgesic. The fact that many of their dosage forms contain aspirin befogs the critical evaluation of these newer analgesics.

Progress in both fields covered by this discussion, namely the volatile anesthetics and non-narcotic analgesics, has been marked. Flexibility in general anesthesia has been increased and anesthetic mortality materially reduced. The non-narcotic analgesics serve well within their field of usefulness. But there is much room for progress. Perhaps with the newer chemical structures leaving the assembly line of the organic chemist, and a more critical evaluation of them as analgesics by the pharmacologist and clinician someday we shall fulfill the Scripture's prophesy, "Neither shall there by any more pain."

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Jackson P. English
American Cyanamid Company
Pearl River, New York

The Chemotherapy of Infectious Disease, 1909–1959

This brief review will deal with the status of the chemotherapy of infectious disease fifty years ago, with its status today, and with the happenings in the half-century between. An attempt is made to present the important things that have been learned, some by-products of interest, the areas of ignorance, and to outline possible goals for the future.

Infectious disease is defined as those disorders of man or animal caused by, or associated with the invasion of the tissue by bacteria, spirochetes, fungi, rickettsia, viruses, protozoa, helminths, and insect larvae. Cancer is excluded. Chemotherapy is the treatment, palliation or cure, and prevention of these infections by the administration of drugs, of natural or synthetic origin, to the host. Those agents which do not act directly on the infecting organism and which affect the symptoms of the infected host as does aspirin for fever and pain or the adrenocorticoids in the case of tissue reactions will be excluded from consideration here.

Other important means of disease prevention must be mentioned so that chemotherapy may be considered in proper perspective. Sanitation and the use of screens or other mechanical barriers between the infection and the host have been of the utmost importance in the control of malarial and helminth infections. The use of insecticides to eliminate arthropod vectors of disease has had a marked influence on the prevalence of malaria, sleeping sickness, typhus, and many other scourges of man and animal. The creation of host immunity through vaccination has been and continues to be the chief method of control for diseases of viral origin. The fact that chemotherapy is an essential, but not the only, weapon in the attack on infectious disease must not be forgotten.

Presented as part of the 50th Anniversary Symposium, Division of Medicinal Chemistry, American Chemical Society, September 16, 1959, Atlantic City, New Jersey.

The Status in 1909

What was the situation in 1909 with respect to knowledge, drugs, scientists, and problems? Some of these factors can be discussed confidently; others require speculation.

It was known that many diseases were of infectious origin. The pioneer work of the brilliant investigators of the nineteenth century had revealed the causative agents of infectious disease. Pasteur and Koch, among others, had shown the bacterial and fungal causes of animal, plant, and human disease. The discovery of the malarial parasite, of the responsible agents of other protozoal disease, and the elucidation of the role of intermediate hosts had been made. The spirochete of syphilis had been recognized. Filterable viruses had been demonstrated as a cause of plant disease in 1892 by Iwanowski and of Foot-and-Mouth disease by Loffler and Frosch in 1897–8 (*1*). The ability of microorganisms of one kind to affect the growth of those of another kind was known to Pasteur. The word "antibiosis" had been coined in 1889 by Vuillemin (*2*).

Biologists were able to produce experimental infections. For example, mice had been infected with the tuberculosis bacillus, pneumococci, and trypanosomes, and rabbits with the spirochete of syphilis before 1900 (*3*).

Drugs of long standing were available to the clinician for the treatment of syphilis, malaria, amebic dysentery, and worm infestations of the bowel (*4*). Mercury for syphilis dated from the middle ages. Cinchona bark for the alleviation of malaria had been known to Western man surely since 1630 and was in wide use after 1700. Ipecacuanha root had been used in South America and the Far East as a treatment for amebic dysentery for centuries. The use of oil of chenopodium and extract of male fern for the treatment of ascarid infections had been known for two thousand years.

Pharmacology had been established as a separate discipline to study the actions of drugs on the body, human, animal, and microorganism in 1863 by Bucheim at Dorpat. An important event in this country was the founding of the *Journal of Pharmacology and Experimental Therapeutics* in 1909.

Organic chemistry had developed phenomenally in the preceding century. The isolation of natural products was a well-established study, Pelletier having isolated pure quinine before 1850. The structure of natural products was being determined, that of quinine having been published in 1909. The inclusion of about 145,000 compounds in the 1910 edition of Richter's "Lexikon der Kohlenstoff Verbindugen" is proof enough of the resources that were available from this discipline.

Some few were working experimentally to find new agents for the treatment of the diseases that imposed a limit to the length of life of man and prevented him from occupying certain parts of the world. Ehrlich and his school had been at work since the 1890's; Morgenroth was active, as was Browning (*5*). This is the roster of groups that were steadily busy at the time in the search for chemotherapeutic agents. They had some support from the organic chemical industries of the day. It is very improbable that as many as fifty people were busy full time in this field throughout the world.

Let us not imagine that the size of the effort was any measure of the sophistication of the work. Ehrlich had elaborated in great detail the bases for successful chemotherapy. The chemotherapeutic index was a valuable experimental tool. The concept that there is no action at a distance, that the infecting organism must be affected directly by the drug, had been enunciated. This firm belief of Ehrlich's was founded upon his observations of vital stains and of the effects of dyes on experimental malaria and trypanosome infections. The knowledge that drugs may be metabolized by the body had been acquired in the case of the arsenicals.

The problem of resistance to drugs had already been encountered in the study of trypanosomiases.

An agent capable of saving mice infected with pneumococcal infections had been found in 1911, by Morgenroth and Levy (*6*), close enough to the beginning of the period under consideration to be counted. The fact to remember is that an experimental bacterial infection had been treated.

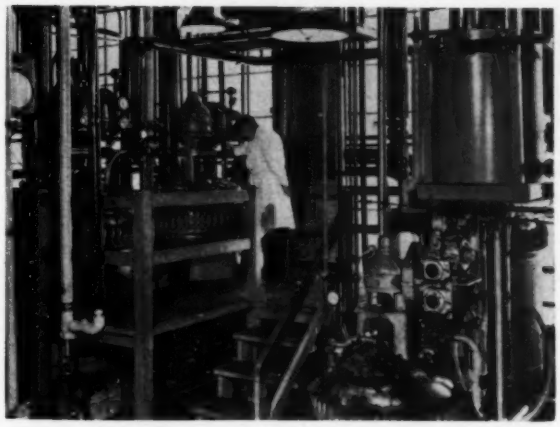
The effect of arsenicals on spirochetal infections was known.

50 Years of Chemotherapy Accomplishment

We now have in penicillin an excellent, safe, and rapidly effective drug for syphilis. The arsenicals developed by Ehrlich had been brought to a higher state of usefulness in the development before being superseded.

Many new drugs have been discovered for the treatment of protozoal infections. The early discovery of germanin and tryparsamide for the trypanosomiases has been followed at a steady rate by other drugs, such as antryeide.

Both systemic and bowel helminth infections have been successfully treated with new agents, hookworm with tetrachlorethylene, ascarids with piperazine, schistosomiasis with antimonials and the Miracils, filiariasis with diethylcarbamazine, and many others (*7*).



One of the four units used in the manufacture of Aralen at the Winthrop plant in Rensselaer, N. Y.

Drugs for the treatment of malaria have been found in great number almost throughout the fifty years under discussion. Chloroquine, primaquine, and daraprim stand out as examples of synthetic agents useful both in the prevention and cure of the disease (*8*).

Drugs for the treatment of the infections of animals with insect larvae have been recently introduced.

Perhaps the most significant accomplishment of the whole half-century, both in its own right and in its stimulating effect on the whole field, was the discovery of the sulfanilamide group of drugs in 1932 by Domagk, which signalized the first effective drug treatment of bacterial infections and the large viruses and encouraged widespread activity in chemotherapy (*9*, *10*).

The antibiotics which were discovered in the rush of activity following the success of the sulfanilamides have given us drugs effective in many diseases. Streptomycin was the first agent of real utility against tuberculosis. Penicillin has already been cited for its effect on syphilis. The broad spectrum antibiotics, chloramphenicol and the tetracyclines, continued the attack on the bacterial diseases and proved effective against large viruses and the rickettsial diseases as well.

Paths to Discovery

The above partial listing is sufficient to establish that many discoveries have been made in the intervening fifty years. It is more interesting and informative to examine the ways in which these discoveries were made than to spend more time in a complete listing.

Why did it take so long to discover the sulfanilamides? Sulfanilamide itself was one of the 145,000 compounds in the 1910 Richter. Mice had long since been infected with pneumococci. Morgenroth and Levy had shown that at least one synthetic compound, optochin, had an effect on the experimental infection in 1911. The reason for trying this compound in the first place is a fine example of how dis-

coveries are made. Morgenroth had observed that both trypanosomes and pneumococci were dissolved by bile acids and affected by quinine and hydroquinine. He then asked, and answered experimentally, the question, "Will optochin affect a pneumococcal infection?" Analogies are always desirable if they lead to experiments (many discoveries have been made in just this fashion).

The series of agents descended from ethylhydrocupreine is of interest for another reason. Work in this series in this country led to the preparation of a derivative from diazotized sulfanilamide and dihydrocupreine in 1919 (*11*). Another twelve years were required to show that compounds of this sort were of value in the treatment of bacterial infections. Why was so much time required? It is probable that two factors worked against the earlier discovery of antibacterial agents effective *in vivo*. The first was the pronouncement of Ehrlich in a talk to the German Chemical Society in 1909 that chemotherapy be saved for the fight against those infections for which vaccines and sera were without effect, such as syphilis and the protozoal infections (*12*). The second factor is the experimental fact that bacteria are too easy to handle *in vitro*. It should be noted that the earliest successes of chemotherapy were scored against those diseases, the protozoal, which *had* to be handled in an animal host.

One is thus led to conclude that the unique aspect of the work of Domagk and his co-workers which culminated in prontosil and led the Tréfouëls, Bovet, and Nitti to sulfanilamide was the fact that the compounds were tested *in vivo*. A similar situation was encountered when one worker concluded that penicillin was of no interest for trial in syphilis as it had no effect in an *in vitro* test against the spirochete, and it remained for Mahoney, who tried the drug *in vivo*, to discover its potential (*13*).

The molecular simplicity of sulfanilamide, the effective part of the prontosil molecule, led to a most important series of events. It re-emphasized the importance of the bodily processes in affecting the composition of a drug as had been the case in the reduction of pentavalent arsenicals to trivalent. The simplicity of the active molecule facilitated the great effort that was undertaken to modify the structure in the hopes of preparing more effective agents. This hope was realized in the preparation of the more active and less toxic sulfapyrimidines in the early 1940's. Sulfanilamide derivatives with modified properties continue to be introduced; for example, sulfisoxazole, sulfamethoxypyridazine, and sulfadimethoxine (*14*).

The success of the sulfanilamides must also be credited with the initiation of the expansion of industrial medicinal chemical research that has occurred since 1937.

It is difficult to describe the most important effect of the discovery of the sulfanilamides on chemotherapy. In my opinion, the demonstration that hitherto deadly diseases could be treated with success established a feeling of confident optimism which has fostered the continuing successes of chemotherapy.

This review is restricted to the scientific and technical aspects of these advances. The beneficial effects of the controlling of many deadly diseases has been great. For example, the tuberculosis sanitarium has begun to disappear as a result, at least partially, of the successful use of streptomycin, *p*-aminosalicylic acid, and isoniazid in the control of the disease. In addition the amount of suffering and loss of time that has been saved due to the sureness and speediness with which pneumonias and septicemias may now be treated is immeasurable.

It is fair to say that the work of Florey and Dubos on antibiotics was stimulated by the successes of the synthetic sulfanilamides. Why else would the original observations of Fleming and others have lain dormant for so long? The advances in therapy that can be credited to the antibiotics have been briefly referred to above.

Another most important contribution from the study of the sulfa drugs has been to methodology. Prontosil was discovered by the testing of compounds *in vivo*. The impetus which was given to random screening by this work has been most important in the continued discovery of chemotherapeutic agents. Random screening has been rejected by some who are active in the field as they feel that it is not a scientific method of working. It is true that random screening does not have the elegance that the design *de novo* of chemotherapeutics agents would have. Yet, I believe that the history of our accomplishments in this field has amply shown that we do not yet have the information or the imagination to design drugs successfully. All of the examples of drug development have had at their beginning the observation of the activity of a lead compound, discovered either in the course of a screening program or by keen incidental observation.

It is worth a little space to consider this important tool. Screening programs designed to find drugs for the treatment of infectious disease fall into three groups. The first and most rewarding with which to work is that in which it is possible to employ the natural host and its infection, as is the case with coccidiosis of chickens. In this type of program there are no biological hurdles between laboratory and the field. In the second group are those which employ a substitute host and the infection of interest as in the use of the mouse or guinea pig and the tuberculosis organism. There are many examples of differences between animal and animal, man included, in sensitivity to drugs. The differences in the reactions of different species to quinine is an example. In the third group, the use of a substitute host *and* a substitute infecting species still further complicates the transition. One need only cite both the toxicities encountered in working with potential drugs for malaria and the species specificity which is shown in the susceptibility to drugs by the human malarias themselves (*15*). The random screening program is still the most powerful tool available with which to answer the question, "What chemical will affect this infection?" It answers it directly by experiment. Random screening need not be intellectually stifling because of the ever-present need to understand and control the biological system and because of the infinity of problems created by the discovery of a lead compound.

The whole field of the chemotherapy of infectious

Solvent used in the production of Aureomycin is recovered in this distillation unit at the Lederle Laboratories in Pearl River, N. Y.

disease has contributed greatly to quantitative biology beginning with efforts of Marshall and his students (*9*). The necessity for the quantitative evaluation of the activities and toxicities of materials of interest has led to the development of statistical tools necessary for the design and analysis of experiments to discover and to compare drugs. The continuing importance of the metabolism of drugs both for their activity against the infection and their effect upon the host has led to application of the most exacting and delicate analytical techniques to the study of drug problems (*16*).

These quantitative techniques have been carried over into clinical studies on human disease as in the clinical studies of drugs sponsored by the British Medical Research Council and the Veterans Administration.

One of the more striking quantitative examples of drug evaluation is in the field of the diseases of economic animals. Here economy of use is of prime importance and cost of treatment must be closely balanced against loss from disease.

The recognition of the activity of sulfaguanidine in avian coccidiosis by Levine, the demonstration by Waletzky and co-workers and Horten-Smith of the economic superiority of sulfamethazine for the treatment of this disease, and the introduction of sulfaquinoxaline by the Merck workers for prevention of the disease by its continuous use in the feed of chickens provide clear examples of drug testing, the use of quantitative methods for drug evaluation, and the application of imagination to the use of drugs (*17*). The use of anticoccidial and of antibacterial agents, antibiotics, arsenicals, and nitrofurfural derivatives have, in the past six years, contributed to a decrease of twenty-five per cent in the time and amount of feed required to raise a broiler (*18*).

Contributions to Discovery in Other Fields

The story of the drugs which have played an important role in the treatment and prevention of infectious disease would not be complete without an examination of the by-products and unexpected findings that have resulted in the course of their study. Four examples of discoveries in other fields that can be traced directly to drugs that were originally developed for the treatment of infectious disease can be cited.

First to be considered is the group of diuretic agents descended from sulfanilamide. Careful observation by Marshall and his group of the effect of this drug on the normal animal revealed an alkalinization of the urine. Following upon this, the role of sulfamyl compounds in the inhibition of carbonic anhydrase was discovered by Keilin and Mann. Deliberate follow-up of this observation by Roblin, Clapp, and Miller showed that variation of the nucleus to which the sulfamyl group is attached could give rise to more potent carbonic anhydrase antagonists and from this study the useful oral diuretic agent, acetazolamide was evolved (*19*). Acetazolamide also has utility in epilepsy and in reducing the intraocular tension of glaucoma. The continued search for more potent diuretic agents in this class has led to chlorothiazide and hydrochlorthiazide as well as ethoxzolamide. The former pair of these are one step farther along the line in that their predominant mode of action is not that of carbonic anhydrase inhibition.

Another descendant of the sulfanilamides is the important class of oral hypoglycemic agents, the benzenesulfonylureas and thiadiazoles. The German investigator, Fuchs, who tried BZ-55 on himself and recognized the symptoms as hypoglycemic in nature when he thought he was trying a long-acting sulfanilamide, gets credit for the one (*20*); Loubatieres in France had followed the thiadiazoles since the observation of their hypoglycemic activity in the early nineteen forties both in this country and in France (*21*). The structural requirement for activity and the resulting modes of action are quite separate from those for the original antibacterial compounds.

Not so directly descended from the sulfa drugs but still owing their beginning to them are the antifolic agents active against tumors. The antimetabolite hypothesis of Woods and Fildes that arose as a result of the demonstration of sulfanilamide-*p*-aminobenzoic acid competition led to the preparation of anti-metabolites by structural modifications of vitamins and essential metabolites (*22*); after the elucidation of the structure of folic acid, one such modification led to methotrexate.

Research in the antimetabolite field led to the preparation of many compounds designed to block the utilization of materials essential for growth. Pantothenic acid analogues have *in vivo* activity against malaria and streptococcal infections but are of no practical use in comparison with other available agents.

One of the more devious trails from infectious disease to non-infectious disease is that which starts from the belief of German investigators that sulfanilamidothiadiazoles were more effective than other sulfa drugs in tuberculosis, leads through the testing of intermediates to the discovery of the thiosemicarbazones as active antituberculous agents. This led workers at Squibb and Hoffmann LaRoche to attempt to make the pyridine analogues (*23*). The testing of intermediates to this compound resulted in the discovery of the still pre-eminent antituberculous drug, isoniazide. A derivative of this compound is iproniazid, at first

discarded as too toxic for use in tuberculosis but now finding clinical application as a psychic energizer, based on the observation of its stimulant activity in patients.

Throughout this period there have been many episodes illustrating the nature of the discovery process. An active curiosity, the ability to plan and the energy to carry out experiments of significance in the testing of imaginative concepts, and the keen observation of *all* effects produced have been common to the discoveries cited. It is important that this process continue. Conscious attention to these factors by workers in the field should improve the yield of discoveries in the future.

Another result of the success of drugs against the infectious diseases has been the change in the nature and amount of support that research has received (*24*). The ability to treat disease economically, in the broadest sense, and therefore, with profit to the manufacturer, has spurred a vast expansion in industrial medicinal chemical research with resulting benefits to human well-being through the contributions of drugs to human and animal health. The public concern in this field has led to the support of research on a vast scale by the Federal Government in this country. The general concern for the protection of the public from harm has led to continuing revisions to the Food and Drug Laws designed to assure responsibility on the part of the manufacturer. All of these interactions are leading to a greater understanding of the problems of disease and the underlying processes of drug action and thus are increasing our chances for the solution of the remaining problems.

Unsolved Problems

What are the unsolved problems of the chemotherapy of infectious disease? How may they be solved? What are the chances for practical solution?

Viruses continue to be the major cause of infectious diseases which we cannot now treat. Those causing the greatest morbidities, colds, influenza, and the like, are so weakly antigenic or, caused by so many different agents, that the probability of complete biological control is small. This is an area in which there must continue to be a concentration of effort to find new drugs in spite of the negative results of a large amount of animal screening to date. The only positive results which have been reproducibly achieved experimentally are the prevention of experimental virus infection by previously administered agents. The intracellular nature of virus infection along with the intimate association of virus proliferation and host cellular biochemistry make this one of the most difficult tasks in specificity that chemotherapy has faced. There is no reason, however, to believe that drugs to treat virus diseases cannot be found.

We are faced with problems of drug resistance in the treatment of bacterial infections, particularly those of staphylococcal origin. No drug to which trypanosomes do not become resistant has been discovered, and Chaga's disease in man is still untreated. We are still unable to treat all gram-negative infections satisfactorily. We have much to learn about drugs and their intimate modes of antibacterial action.

Drugs active against a large number of helminth infestations are rare. Still undiscovered are drugs to treat infestations of helminth larvae. The many successful agents that have been found for the treating of infection by adult worms ranging from filiariasis to ascarid infestations have been inactive on the larvae. The latter are frequently the most harmful form of the parasite, as in the ascarid pneumonia of man and swine, and in trichinosis. Again there is no reason that agents for the eradication of these larvae cannot be found with continued work.

In addition to the highly practical goals outlined above there is the constant need to expand our knowledge of the known effective drugs, and of the biochemistry and physiology of host and infecting agent so that the ultimate goal, the *de novo* design of drugs will eventually be reached.

In summary, 1909 and 1959 are not far apart qualitatively but differ a great deal quantitatively. The tools, in more rudimentary form, perhaps, were known fifty years ago. The problems were all in existence. Some forerunners of success in each of the broad fields in which we now have useful chemotherapeutic agents were known. We differ from 1909 in the number of people engaged by at least one hundredfold and in our greater confidence. Let us not lose it.

Acknowledgment

I wish to acknowledge the assistance of my colleagues of the profession for the information furnished and their patience in discussion which has made this review possible. My sincere apologies are tendered to the numberless investigators whose contributions have not, for reasons of space, been noted but which are, nevertheless, as important as those that have been mentioned specifically.

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Roger J. Williams
University of Texas
Austin, Texas

Vitamins as Medicinal Agents

In the earlier pharmacopoeias the medicinal agents listed were largely those that had been found empirically to be useful– or at least they were thought to be useful. Since most of the chemistry in the body is under the mediation of specific enzymes, it may be presumed that the vast majority of these agents are effective, if at all, because they interfere somehow and somewhere with enzyme-catalyzed reactions. Particularly is this so of such agents as alkaloids, glucosides, and synthetic chemicals which are foreign to mammalian organisms. Prolonged use of such agents is inherently dangerous.

The vitamins as well as the nutritionally effective minerals and amino acids belong in quite a different category in that they are characteristically effective in a constructive way. Many of these are definitely known to be essential parts of enzyme systems, and many others may be presumed to be. Hence their ingestion contributes raw materials essential for the building of necessary catalysts and they may be taken in suitable amounts for an indefinite period without danger.

Those who are in the field of medical practice are often not fully aware of the distinction between foreign agents which have been found empirically to be effective and those agents which are known to be constructive in their action. For example, a physician recently discussed with me the relative merits of physostigmine and calcium pantothenate in the treatment of *paralytic ileus*. He had tried both agents and had a preference for the latter, but this was strictly on the basis of practical trials. The fact that pantothenate must act constructively (i.e., nutritionally) evidently did not enter into his thinking. Several years ago one of my graduate students found that taking calcium pantothenate definitely prevented his allergy for plants in a certain desert region. When this corroborated finding was submitted for trial, calcium pantothenate was compared with an antihistaminic as an antiallergy agent. The calcium pantothenate was found beneficial, but was not able to show up well in competition with the antihistaminic and the usefulness of the constructive agent was not promoted.

There is evidence that pantothenate administration in some individuals relieves constipation, but again in this case the fact that it must function nutritionally is overlooked, and it must compete on an equal basis with phenolphthalein, cascara, magnesium sulfate, and other drugs which are effective because they are noxious.

My colleague, Dr. William Shive, has found that glutamine (a natural amino acid which enters extensively into numerous metabolic processes) promotes healing in stomach ulcers. In order to convince the experts of its value, however, it must be compared with antispasmodics which of course are not constructive in their action but may interfere with nerve responses in such a way as to be practically beneficial. Glutamine on the other hand must act as a nutritional agent.

A point of view which is commonly held by many incompletely informed professional men is reflected in the advice: "Nutrition comes from food. Eat good wholesome food and nutrition takes care of itself."

This view which would discourage the medicinal use of vitamins and other nutritional elements needs to be examined from a number of angles. There are, briefly, five reasons why the neglect of these medicinal agents which are constructive in action, can contribute to ill health:

1. Refinement and processing of food incident to its storage and transportation may make it lose its ideality. In our day food is often produced long distances from its point of consumption and long times intervene between its production and its use. Despite

Presented as part of the 50th Anniversary Symposium, Division of Medicinal Chemistry, American Chemical Society, September 16, 1959, Atlantic City, New Jersey.

relative effectiveness of our operations, no one can claim that our food is of exactly as high a quality as it would be if we lived closer to nature.

2. Individuals may not possess effective regulating mechanisms which make it possible for them to choose foods wisely. The wisdom of the body is an important factor in maintaining good nutrition, but some individuals who are not endowed with good regulating mechanisms eat too generously, have too much of a craving for sweets, have a tendency to consume too much fat, or have a strong craving for alcohol. No amount of sage advice or lecturing takes the place of a built-in automatic regulatory mechanism. Sedentary lives which are commonly led probably contribute to transform "body wisdom" into "body foolishness."

Nutrition is far more complicated than is commonly appreciated. When what we call differentiation takes place during embryonic development, the daughter cells eventually become very different from the original mother cell—different in size, shape, composition, metabolism, *and in nutritional needs.* Recent tissue culture studies make it evident that different tissues do not have the same nutritional needs and that some cells require nutrients (glutamine, for example), which are not needed by the body as a whole. Some cells in the body must produce glutamine, in this instance, which acts as an essential nutritional substance for other cells. The most adequate nutrition we can attain is one in which all of the functioning cells and tissues get, directly or indirectly, ample supplies of everything that they need. This is a large order, and one can have no assurance that maximum bodily health can always be maintained simply by more or less haphazard consumption of what is regarded "good wholesome food."

3. Individual people are often subjected to mild poisoning agents, to infections, and to excessive psychological stress. All of these influences may augment specific nutritional needs. If these influences were not in their lives, perhaps "good wholesome food" alone would be highly satisfactory. When these factors are taken into account, it is not obvious by any means that nutritional needs can be completely met automatically. In individual cases there is often a need for special attention.

Millions of gelatin capsules are produced on these machines at the Parke, Davis plant in Detroit.

4. Recent advances in the field of biochemical genetics led by the Nobel Prize winners Beadle, Tatum, and Lederberg make it inescapable that different individuals have nutritional needs, including those for vitamins, which are quantitatively different and distinctive. Some individuals, it follows, have unusually high requirements for specific nutrients. For these individuals "good wholesome food" may not be enough. Their diets may require special attention in order that all the operating cells and tissues of their bodies shall not only be nourished but well nourished.

Let me cite some examples of recent data collected in our laboratories by my associate, Mr. Richard Pelton.

Industrial beehives, this bank of 36-inch molecular distillation units is used for the production of vitamin A and E concentrates at the Distillation Products Industries Division of Kodak.

Individual white rats such as are often used for nutritional experiments were subjected to a regimen where they individually had choices of food, drink, and exercise. Among the variations observed in a relatively small group of "uniform" rats, mostly over a nineteen-day period, were the following:

One rat ate 7 times as much butter as another
One rat ate 17 times as much sugar as another
One rat drank 15 times as much alcohol as another
One rat ate 45 times as much fortified yeast as another
One rat excreted 10 times as much urine as another (water given *ad lib.*)
One rat excreted 100 times as much phosphate in the urine as another (In this case they were on the same diet.)
One rat's exercise was the equivalent of traveling 150 feet a day; at the other extreme, one rat averaged 6 miles per day.

If experimental rats vary this much, it seems that human beings with far more diverse genetics vary much more. We have a real reason for our belief that biochemical individuality enters as an important factor in our lives, in our eating, and in the satisfaction of our bodily needs.

5. During the process of aging, individuals may develop augmented needs which did not exist during youth. Those who prosper on "good wholesome food" during their younger years may need to pay more strict attention to their special needs as they age.

I must stress the need for further research with respect to the medical and non-medical use of vitamins and other nutrients. What is being done in this area now is done too often in a hit or miss manner.

Albert J. Plummer
and **Fredrick F. Yonkman**
CIBA Pharmaceutical Products Inc.
Summit, New Jersey

Antihypertensive and Diuretic Agents: Past, Present, and Future

It is appropriate that a review of the recent progress in the drug therapy of essential hypertension should be included in the Fiftieth Anniversary Program of the Medicinal Chemistry Section of the American Chemical Society, because practically every advance in this field has been achieved within the span of the past half century. In 1732 an ingenious experimental measurement of the blood pressure of a mare was reported to the Royal Society of London by Stephen Hales. In this classic experiment the height of the pulsating column of blood, and hence the pressure, was measured by means of a vertical glass tube which had been inserted into the cervical artery of the horse. Hales observed that the horse became uneasy during the experiment, which is not too surprising. The technical difficulty, danger to the patient, as well as the impact of the experience upon the level of the blood pressure itself, precluded the general use of such direct measurement of human blood pressure. Actually, it was not until the early part of the present century that a simple, safe, and reliable technique was devised for the determination of human blood pressure. This was accomplished in 1905 by Korotkow, who developed the now well-known auscultatory method based on a combination of the occluding blood pressure arm cuff and the stethescope. Widely used over the world in the intervening years, this technique has served a dual role which not only highlighted the incidence of elevated blood pressure in the population but also revealed its serious consequences and the reduction of normal life expectancy in those afflicted with the disorder. In fact, cardiovascular disease, commonly due to hypertension, with its sequelae—arteriosclerosis, kidney disease, cerebral hemorrhage, and coronary artery disease—is the leading cause of death in the adult population at the present time.

Early Views on the Treatment of Hypertension

Progress in the therapeutic management of hypertension was not rapid during the early part of the century, partly because the etiology was unknown, but to a larger extent because a prevailing medical viewpoint held that elevation of the blood pressure was a protective compensatory adjustment to an ill-defined increase in the circulatory demands of the organism. Such an hypothesis would not, of course, foster the quest for the means to alleviate the situation. The available therapeutic resources of even a decade ago did not provide the opponents of this opinion a fair opportunity to test its validity since the few drugs which were in use at the time had been developed on an empirical basis and possessed little if any of the requisite pharmacological properties for modifying the existing hypertensive state. Within the past decade, as a result of a rational and intensive research program fostered jointly by the pharmaceutical industry and the medical profession, more progress has been made in providing effective and specific drug therapy for the treatment of human hypertension than had been previously attained in the centuries since Hippocrates. These recent advances in the drug treatment of hypertension are the more remarkable when it is realized that the underlying etiology of essential hypertension remains a baffling mystery. Much has been learned about the nature of the disorder, however, and a brief discussion of this aspect must necessarily precede a clear understanding of the utilization of sound pharmacological principles which has led to the development of a group of specific and potent antihypertensive agents.

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Factors Underlying the Development of Hypertension

There are several factors responsible for the maintenance of normal human blood pressure. However, the elevation of the blood pressure in essential hypertension is related to a deviation in but one of these controlling factors. Specifically, the caliber of the arterioles or smaller arteries is narrowed, thus causing an increase in resistance to the flow of blood. The etiology of the arteriolar constriction or narrowing is unknown. In any case, the resulting increase which takes place in the arterial blood pressure eventually produces a compensatory increase in the thickness of the arterial wall which further narrows the bores of the blood vessels. Ultimately, secondary degenerative changes, including atherosclerosis (the deposition of cholesterol and lipoid material in the arterial wall) and arteriosclerosis seriously interfere with the blood supply to vital areas, notably the heart, brain, and kidney, thus leading to irreparable damage to these important organs. The inadequate circulation not only damages the kidney but may also cause an increased output of renin, which by cleaving certain proteins of the globulin fraction, leads to an increased production of hypertensin, a powerful arterial vasoconstrictor. At this stage renal hypertension is superimposed upon the pre-existing hypertension. There are some authorities who feel that such a renal factor may be of etiological importance in essential hypertension. However, there is no conclusive evidence that this is the case. In fact, in the early uncomplicated case, increased vascular tone and resistance

appears to precede rather than follow any pathological changes in the kidneys.

The combination of narrowed and weakened blood vessels with high intra-arterial pressure, carries with it the danger of rupture leading to cerebral hemorrhage with its grave prognosis. The heart is rendered especially vulnerable by a vicious chain of events. The cardiac muscle hypertrophies (increases in size) as a result of the increased work which must be performed against an elevated pressure. The increased muscle mass consequently requires a richer blood supply while the coronary vessels which must transport the blood become progressively more narrowed and sclerosed. When the coronary blood supply is sufficiently embarrassed, cardiac failure results. Similarly, sclerotic changes in the renal blood vessels lead to progressive reduction in the functional capacity and reserve of the kidney. It is not surprising, therefore, that the incidence of heart disease, cerebral hemorrhage, and kidney disease is high, and life span is reduced in those with abnormally elevated blood pressure.

There is much uncertainty as to the relative importance of constrictor nerve overactivity or of circulating hormonal substances in provoking the initial arteriolar spasm observed in essential hypertension. It may well be that both mechanisms are involved and that an initial spasm evoked by one means may activate, and, in turn, be reinforced by the other. It has long been realized that man, by his thoughts alone, can elevate his blood pressure. On this basis it has been proposed by Schroeder that anxiety and tension may precipitate a rise in blood pressure which is mediated by nervous impulses traveling over vasoconstrictor nerve pathways extending from the brain to the peripheral blood vessels. The reduced renal blood flow thus induced may lead to the formation of excess circulating vasoconstrictor substances, probably through the mediation of increased renin liberation, resulting in still more narrowing of the blood vessels. A positive feedback is thus set up which is initially temporary in its effect, but later, upon repeated recurrence, becomes fixed and permanent as structural alterations in the arteries supervene. The administration of certain adrenocortical steroids leads to the development of hypertension in animals. Green favors the view that since the effect of repeated administration of adrenal corticosteroids to animals closely resembles the pathological picture of essential hypertension, especially with respect to sodium retention, an excess of such hormones may be of etiological significance. Whatever the original cause may be, the most satisfactory results in drug therapy have been obtained by agents which reduce the predominance of the vasoconstrictor influence of the sympathetic nervous system. This is not to imply that the primary focus of the disease has been attacked, but rather to indicate that these agents provide access to a vulnerable point in the armor of a most resistant pathological entity.

Importance of Sympathetic Nervous System in Blood Pressure Regulation

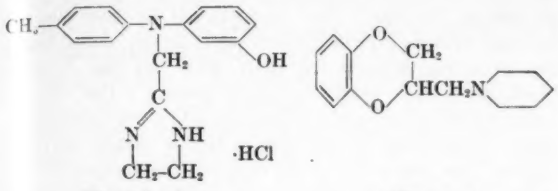
The clue to the application of the principle of reduced sympathetic predominance for the amelioration of essential hypertension was provided by Peet and Smithwick, who showed that the surgical interruption of sufficient efferent sympathetic nervous pathways resulted in a prolonged drop in blood pressure. In this operation, which is known as a sympathectomy, bilateral excision of the thoracolumbar sympathetic ganglionic chains, together with the splanchnic nerves, reduced vasoconstriction and vascular resistance sufficiently to lower the mean arterial blood pressure significantly. Moreover, Raab has demonstrated a decrease in the heart catecholamines following sympathectomy. This accomplishment has been a stimulus for the development within slightly more than a decade of a number of compounds intended to provide a so-called pharmacological sympathectomy.

There are several specific junction points along the sympathetic pathway at which a drug may exert a suppressant effect on the autonomic nervous system. They are (1) the junction between the nerve and the blood vessel, (2) the junction within the sympathetic ganglia, and (3) the sympathetic center within the midbrain. In addition, other less well-defined areas of the brain may be involved, and, finally, the responsiveness of the smooth muscle of the peripheral blood vessels to nervous stimulation may be altered.

Antihypertensive Action of Agents Blocking the Sympathetic Nervous System

Adrenergic Blocking Agents. Substances which act at the junction between the nerve and the blood vessel were the first to be tried in the modern treatment of hypertension. Historically, these were the first available. Their action could be readily detected in the experimental animal because of their property of reversing the pressor effect of epinephrine and of markedly reducing the blood pressure rise produced by norepinephrine. Ergotoxine had been known to possess this action, known as adrenergic blockade. However, the powerful vasoconstrictor action of the substance itself overrode the blockade and actually resulted in a hypertensive effect. The yohimbine alkaloids also caused adrenergic blockade and were hypotensive, but their efficacy was marred by a strychnine-like central stimulating action. Dibenamine exhibited strong and long-lasting adrenergic blocking effect but was found to be too toxic for safe clinical use. Phentolamine and piperoxan proved to be the most specific and interesting compounds of this type. When applied in the treatment of essential hypertension, however, they were disappointing, chiefly because they did not impede the adrenergic cardioaccelerator nerves to the heart. The resultant rapid heart rate and increased cardiac effect were physiologically disadvantageous, and, in addition, tended to combat any possible hypotensive effect. These substances, have, however, found a very important clinical application in the diagnosis of pheochromocytoma, an adrenal tumor which secretes excessive amounts of catecholamines into the circulation, resulting in an increase in blood pressure which falls dramatically when small amounts of these adrenergic inhibitory substances are injected intravenously. In contrast, essential hypertension is resistant to these compounds. It is thus possible to diagnose the presence of this type of tumor. In addition, it is also possible, by means of such blocking agents, to protect the patient against

the deleterious effects of excess catecholamines which are expressed into the circulation during the operative removal of the tumor.



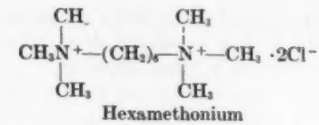
Phentolamine

Piperoxan

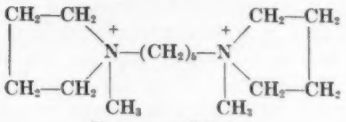
Ganglionic Blocking Agents. The next group of substances to receive attention as possible antihypertensive agents was the ganglionic blocking agents which block the sympathetic nervous pathways at the ganglionic junction. Actually, the pharmacological action of these substances appears to be based on a competition with acetylcholine for a site on the receptor substances of the postganglionic nerves. These substances, represented by hexamethonium, pentapyrrolidinium, chlorisondamine, and mecamylamine, are remarkably effective hypotensive agents, and, because they interrupt the cardioaccelerator nerve impulses, they do not give rise to the annoying tachycardia associated with the adrenergic blocking agents. Hexamethonium and pentapyrrolidinium are bisquaternary compounds in which the distance between the onium centers is occupied by either five or six carbon atoms. Bisquaternary compounds as a class are not well absorbed orally, and for this reason, a search was made for agents which would be more readily absorbed. Chlorisondamine, an interesting outgrowth of this search, represents a departure from the chemical constitution of the other ganglionic blocking agents in several respects—(*a*) the distance between the onium centers is reduced to two carbon atoms, (*b*) it is unsymmetrical, and (*c*) tetrahalogenation of the heterocyclic nucleus has been carried out. This latter alteration appears to be the most important factor in providing the increased potency and duration of effect and improved oral efficacy characteristic of chlorisondamine. Mecamylamine, another recently-developed ganglionic blocker, is a secondary amine rather than a quaternary derivative, a variation which has contributed to increased potency and improved oral effectiveness in this substance.

The principal disadvantage of such compounds is their lack of specificity, since they block the parasympathetic ganglia as well and cause visual disturbances, dryness of the mouth, constipation, and impotency as a consequence. The tendency to cause marked postural hypotension, or dizziness upon assuming the erect position, has posed a problem in therapeutic management which has not been adequately solved and has interfered with the more favorable development of this type of drug. The practice in the United States has been to resort to ganglionic blockade primarily for the treatment of malignant hypertension, and when other milder and better-tolerated agents are not effective.

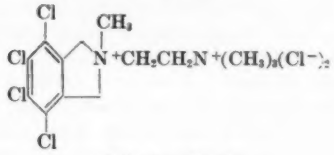
Hydralazine. Historically, hydralazine or 1-hydrazinophthalazine, was the next synthetic substance to assume prominence as a therapeutic agent in the management of hypertension. First employed in 1952



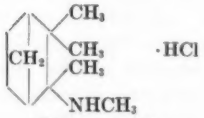
Hexamethonium



Pentapyrrolidinium

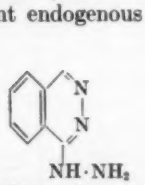


Chlorisondamine



Mecamylamine

for this purpose, it has been used widely since as an effective antihypertensive drug. In the experimental animal, hydralazine causes a gradual and sustained drop in blood pressure. Its action, however, is not referable to a single point of attack as with the adrenergic and ganglionic blocking agents. Its primary site of action was originally believed to be within the brain, since its hypotensive effect was eliminated when the brain centers were neutralized by high transection of the cord. However, it was later learned that the vasoconstrictor effect of substances such as ergotamine and ephedrine, agents known to act peripherally, were antagonized by hydralazine after cord transection. In addition, the substance was found to antagonize the pressor effects of epinephrine and norepinephrine to a moderate degree. In fact, the dilator effect of epinephrine on the coronary arteries was augmented by hydralazine, as shown by Barrett. It has also been noted by Reubi that hydralazine increases the renal blood flow in both animals and man, presumably by its antagonism of the vasoconstrictor effect of norepinephrine. Correction of renal ischemia (reduced renal blood flow) *per se* could be of positive advantage in eliminating a possible etiological factor in hypertension. In fact, Gaunt has shown that hydralazine prevented the damaging effect of renin, a substance produced by the ischemic kidney, on the whole vascular system and especially on the kidney. The action of histaminase is inhibited by hydralazine, thus reducing the rate of destruction of a potent endogenous capillary dilating substance.



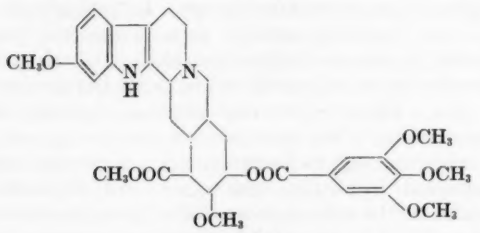
Hydralazine

The unique character of the action of hydralazine is the manifold and varied mechanisms by which it can act to lower blood pressure. In any case, the net

result is a dampening of the activity of the sympathetic nervous system with a resultant drop in arterial resistance and reduction in blood pressure.

Veratrum Alkaloids. Attempts were made to utilize the hypotensive actions of the veratrum alkaloids in the treatment of essential hypertension at about the same period that hydralazine was being tested. These substances act by a complex and not too completely understood mechanism. Their site of action is in the heart and lungs, where they inactivate certain nervous receptors whose normal function is to send impulses to the brain whenever the blood pressure is above normal. The brain, in turn, brings about a reflex decrease in the degree of constriction of the arterioles with a resultant fall in blood pressure. However, from a practical standpoint the amount of drug which lowers the blood pressure is very close to the emetic dose, and, for this reason, these substances have not found the general usefulness which they might have achieved.

Reserpine. The use of the Rauwolfia serpentina plant in the treatment of hypertension followed closely upon that of hydralazine. This plant had been renowned in Indian medicine for centuries for its calming effect, but it was not until 1949 that Vakil, an Indian physician, ascribed antihypertensive action to it on the basis of clinical experience. Three years later, Mueller, Schlittler, and Bein provided unequivocal evidence in the experimental animal of such action in an alkaloid which they isolated and named reserpine.

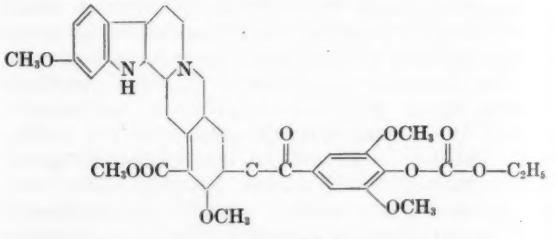


Reserpine

Prior to that time the numerous alkaloids obtained from the plant had shown no such activity.

The mechanism of the hypotensive action of reserpine has been investigated in many quarters in the relatively few years since its isolation. It was apparent to Bein that the various pharmacological effects of reserpine, such as hypotension, lowered pulse rate, constricted pupils, quietude and relaxation of the nictitating membrane (the third eyelid of animals) were consistent with a reduction of the activity of the sympathetic nervous system. The weight of evidence indicated that this reduction of sympathetic dominance originated within the central nervous system. When Pletscher, Brodie, and Shore found that reserpine acted to deplete serotonin from various structures, it was suggested that this alteration might provide a biochemical basis for both the sedative and hypotensive effects of the alkaloid. However, the subsequent observations of Holzbauer and Vogt and of Carlsson that reserpine released norepinephrine from the brain and peripheral structures raised the question of the mechanistic importance of the depletion of this amine whose principal function is to constrict the blood vessels. It is now generally agreed that this latter effect is the more important for the blood-pressure lowering action of reserpine. However, since the liberation of the catecholamines by reserpine occurs in the hypothalamus as well as peripherally, it is probable that the dampening of the sympathetic nervous system is related to both its central and peripheral actions. The importance of the central nervous system for the hypotensive action of reserpine has been emphasized by Bein, who has shown that blockade of the carotid occlusion pressor reflex can be achieved with intravenous doses of 50 to 100 microgm./kgm of reserpine in the dog with an intact nervous system, but that subsequent to brain transection in the region of the mammillary body, the carotid occlusion reflex reappeared and now required a dose of reserpine ten to twenty times as great for antagonism of the reflex. Since the hypotensive effect of reserpine seen in the laboratory is reflected in clinical antihypertensive efficacy, it is apparent that depletion of the sympathetic neuroeffector substance from the sympathetic nervous system and the heart is a desirable criterion for the potential worth of a substance in the management of essential hypertension.

Syrosingopine. Considerable effort has been expended in an attempt to modify the chemical structure of reserpine so as to retain the hypotensive while excluding the sedative component. One compound, which has been synthesized by Lucas in this attempt, deserves mention because of its interesting properties. It differs from reserpine in having a carbethoxysyringoyl group instead of a methoxy group in the para position of the trimethoxybenzoate section and has been given the generic name, syrosingopine.

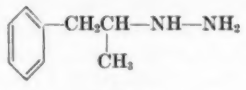


Syrosingopine

This change has had little influence on the hypotensive aspect but has strikingly reduced the sedative properties of the naturally-occurring alkaloid. The latter effect is but one-tenth to one-fortieth that of reserpine as measured in various animal species. Clinically it has been possible to exploit the properties of syrosingopine in the treatment of hypertension where sedation is not necessary. Orlans, Finger, and Brodie have recently provided a biochemical explanation for the observed division of hypotensive and sedative effects. This group has found that syrosingopine is capable of markedly reducing norepinephrine in the heart of animals in doses which do not significantly remove either this amine or serotonin from the brain. It thus appears from these results that syrosingopine, and probably reserpine as well, exhibit hypotensive activity by virtue of depletion of norepinephrine. The freedom from sedation seen in the case of syrosingopine may, of course, be related either to its failure to enter the brain or to influence the amines present in the brain upon entry. Since some sedation can be demon-

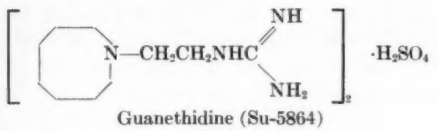
strated with extremely high doses of syrosingopine, it would appear that access to the brain can be gained, but much less readily than in the case of reserpine. The synthesis of syrosingopine, therefore, has provided a suppressant action on sympathetic nervous vasoconstrictor tone with a greater specificity of effect than was previously available.

Catron. Catron, or phenyl isopropyl hydrazine, an inhibitor of amineoxidase, has also shown hypotensive action in animals which suggests a potential application as an antihypertensive agent. It is not certain, however, that the enzymatic inhibitory effect bears any causal relationship to any effect of Catron on the blood pressure, and the exact mechanism of its action remains to be elucidated.



Catron

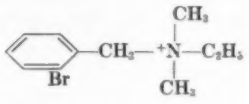
Guanethidine. Recently a guanidyl derivative, synthesized by Mull, has shown an interesting type of inhibitory action on the sympathetic nervous control of the cardiovascular system.



Guanethidine (Su-5864)

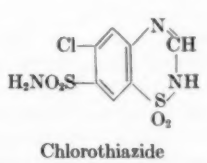
Maxwell noted a delayed hypotensive effect and blockade of the nervous reflexes controlling blood pressure which developed several hours after the injection of guanethidine and lasted several days. This effect was markedly greater in the neurogenic and renal hypertensive dog than in the normotensive animal. An analysis of its activity revealed a relaxation of the nictitating membrane and a potentiation of the pressor effect of norepinephrine. Both of these actions are shared by ganglionic blocking agents, and the former is also associated with adrenergic blocking agents. However, neither of these stated mechanisms sufficed to explain the action of guanethidine, since ganglionic transmission was normal and since the nictitating membrane contracted normally in response to the injection of norepinephrine. This suggested the possibility of an interference with the liberation of the sympathetic vasoconstrictor principle at the nerve terminals. An early period of restlessness, less intense but not unlike that seen with reserpine in the dog, suggested the possibility of release of norepinephrine by guanethidine. In contrast to reserpine, no subsequent state of sedation developed. Studies by Sheppard indicate that norepinephrine is, in fact, removed from the heart and the spleen. The correlation of this effect and observed pharmacological action is under investigation. Interference with the liberation of norepinephrine at sympathetic nerve endings may also play some part in the action of guanethidine. From a practical standpoint, the most intriguing aspects of the action of guanethidine are remarkably prolonged action after a single oral dose, together with a more intense action in the experimental hypertensive animal than in normal controls. Effective and prolonged hypotensive action in the human has also been noted in the clinical studies of Page, Freis, and Richardson. Since guanethidine affects the sympathetic nervous system to the exclusion of the parasympathetic nervous system, it does not cause blurred vision, dryness of the mouth, or impotence, such as may be experienced when ganglionic blocking agents are employed.

Bretylium. Also recently, a benzyl quaternary compound known as bretylium has been found to reduce the reactivity of the sympathetic nervous system and to display hypotensive action. Bretylium has the following chemical formula:

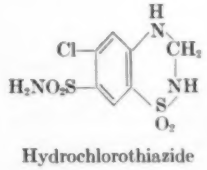


It is said to accumulate selectively in adrenergic nerves and to block nervous transmission in them. Neither ganglionic blockade, adrenergic blockade, nor central sedation are found among the effects of bretylium. The modes of action of guanethidine and bretylium appear to be by different mechanisms, although in the same general area of the peripheral sympathetic nerves. Bretylium has also shown antihypertensive action in the human. The most distinctive difference in the actions of the two compounds lies in the prolonged duration of action exhibited by guanethidine. The specific mechanisms of action of these substances at a biochemical level will require further study.

Diuretics as Antihypertensive Agents. The recently-developed sulfonamide diuretics typified by chlorothiazide, synthesized by Sprague, and hydrochlorothiazide, synthesized by de Stevens and Werner, have also been classed as antihypertensive agents clinically by Freis, Wilkins, and Hollander. It is of interest that hydrochlorothiazide, which differs from chlorothiazide only by the elimination of a double bond is ten to twenty times as potent as a diuretic and is also of a longer duration of action than chlorothiazide.



Chlorothiazide



Hydrochlorothiazide

There is some question as to whether the antihypertensive action of such compounds is secondary to the elimination of sodium from the circulation and from the walls of the blood vessels or whether it is a direct action of the sulfonamide on the blood vessels themselves. However, the antihypertensive effect appears undeniable and is utilized to best advantage when the diuretic agent is employed in conjunction with the specific antihypertensive agents previously mentioned. In this connection it has been definitely shown by Barrett that hydrochlorothiazide is capable of potentiating the antihypertensive actions of hydralazine, while Gross has shown intensification of ganglionic blockade by hydrochlorothiazide. Of interest, and probably of some significance in the treatment of hypertension, it has also recently been learned by Gross that hydro-

chlorothiazide is capable of antagonizing the blood pressure-raising effects of epinephrine and norepinephrine, the neurohumoral vasoconstrictors of the sympathetic nervous system, and of hypertensin, the hypertensive factor whose origin is traceable to the kidney. It thus appears that hydrochlorothiazide may exert its antihypertensive effect in part by altering the reactivity of the vasculature to norepinephrine and other biologically active endogenous substances, but the fundamental mechanism by which this action is brought about may still be related to its more specific action of decreasing sodium resorption by the renal tubule. In this connection, Raab demonstrated an augmentation of the pressor effect of adrenergic substances in humans receiving desoxycorticosterone with and without increased sodium intake, and Gross and Lichtlen recently have noted a heightened sensitivity of rats pretreated with desoxycorticosterone and sodium not only to epinephrine and norepinephrine but also to renin, hypertensin, and vasopressin. One possibility suggested by Gross for these observations is an increased sensitivity of the arterial system to hypertensive stimuli due to a higher sodium, potassium, and water content of the arterial wall. The observation by Gross of a retardation by hydrochlorothiazide of hypertension induced in rats by desoxycorticosterine is consistent with this hypothesis since this type of hypertension is intimately linked with sodium retention. Significantly also, hydrochlorothiazide is not effective against hydrocortisone-induced or renal hypertension in the rat, probably because these conditions are not dependent upon increased sodium in the diet.

Though the etiology of essential hypertension remains uncertain, there is evidence that a defect in electrolyte excretion commonly becomes manifest at some point in its course. At such a time the changes in vascular composition and reactivity mentioned above might ensue, and, as a result, lead to further peripheral resistance due to "water logging" of the arterioles as proposed by Tobian.

Summary

Despite the remarkable strides made in the acquisition of effective antihypertensive agents within the past decade, it is equally certain that efforts now in progress in the various laboratories will ultimately result in drugs which will be even more effective in the therapeutic management of essential hypertension. From present results and past experience, it would appear that future advances in the antihypertensive field are most likely to result from the continuing investigation of agents which dampen sympathetic nervous activity. It would be presumptuous to state that depression of the autonomic nervous system is the only avenue of approach to the problem of the therapeutic management of hypertension, but until now it has been the most fruitful and has not as yet been explored to the ultimate.

Lewis H. Sarett
Merck Sharp & Dohme
Research Laboratories
Rahway, New Jersey

The Hormones

The word "hormone" was coined by W. Hardy working in the laboratory of the English physiologist, Ernest Starling, in 1905 and was designed to be the Greek equivalent of the phrase "chemical messenger." Since hormones are the chemical agents secreted by the ductless glands, and since they act specifically on other target tissues, their identity as chemicals on the one hand and as "messengers" on the other is very reasonable. There are twenty-eight currently accepted mammalian hormones. This is a figure twice as great as the number of identified vitamins. This suggests that for a truly exciting life, a balanced diet is only half the story.

The clear-cut anatomical and histological differentiation of the ductless glands prompted rudimentary exploration on their effects in the earliest times. The greater tractability of the ox and the gelding in agricultural practice was a pre-Biblical discovery. In a sense the identification of the hormone testosterone by Laqueur in 1935 was the culmination of a experiment which in one form or another had run for more than twenty centuries.

It has been pointed out that most of the hormones are not really essential for existence. Rather they appeared with the phylogenetic evolution of man and enabled him to respond in a more complex fashion to his environment. In spite of this dispensibility of most of the hormones for physical existence, it is certainly true that man's progress at the social level would be hampered by their absence. Consider the sluggishness of the cretin and the indifference and languor of the Addisonian.

In agreement with this role of facilitating homostatis, the hormones are secreted in response to specific temporal or environmental stimuli. In contrast with the energy-producing metabolic mechanisms which roll on in splendid and ceaseless autonomy, most of the endocrine responses are discontinuous ones. The major part of the secretion of growth hormone is accomplished

Presented as part of the 50th Anniversary Symposium, Division of Medicinal Chemistry, American Chemical Society, September 16, 1959, Atlantic City, New Jersey.

during the first fifth of the life span. The gonadotropic secretion, on the other hand, only starts at about the time that growth hormone slows up. Aldosterone release is triggered by low serum sodium levels; epinephrine and hydrocortisone by stresses from appropriate environmental stimuli, and so on. The construction of this picture of marvelously regulated responses to a complex environment is undoubtedly one of the great triumphs of biological science over the past fifty years.

The hormones are the most potent class of biologically active agents in existence. Only lysergic acid diethylamide, Vitamin B_{12}, and one or two other agents are effective in such low doses. Starting at the weaker end of the scale the steroid hormones progesterone and hydrocortisone are the two feeblest, 25 mg being the average daily amount required for normal function. In order to maintain normal carbohydrate metabolism only 1–2 mg of insulin is required per day. The difference between normal growth and pituitary dwarfism is only a milligram or so of growth hormone daily. The estrogens begin to get into the more potent range of the spectrum. Hoskins has calculated that if the human were as sensitive to estrogens as the rat, an effect could be elicited from every female on the North American continent with a total of one ounce of estrone. On the extreme end of the potency scale we find glucagon, vasopressin, oxytocin, epinephrine, and the corticotrophin-regulating factor. An essentially weightless invisible residue amounting perhaps to 10^{-5} mg will elicit the full-blown effect of these substances—increase in blood pressure, release of adrenal steroid, induction of labor, and so on.

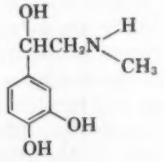
The extraordinary sensitivity of the receptor site is another important aspect of the potency problem. It is perhaps, a matter of greater wonderment that so exquisitely sensitive a receptor can be fashioned, as that so little of an activator can set it off.

The hormones have achieved a place in medicine. Fourteen are in routine clinical use, especially in the treatment of deficiency states in which an inadequate amount of endogenous hormone is available. Only three of the hormones are fully active by the oral route: thyroxine, hydrocortisone, and estrone. Three others—testosterone, progesterone, and epinephrine by synthetic modifications have been converted to orally active analogues. The balance have had to be used parenterally, with emphasis going into longer-acting and repository dosage forms. The importance of the hormones to clinical medicine can conveniently be measured in terms of the annual U. S. sales volume at the manufacturer's level. In order of importance they range from hydrocortisone and analogues—$100,000,000 (dermatoses, rheumatoid arthritis, lupus, rheumatic fever) through insulin—$20,000,000 and the estrogens—$20,000,000 to oxytocin—$600,000 and gonadotrophine—$150,000.

Origin of Hormone Research

Prior to 1900 a few isolated pieces of evidence existed which quite clearly indicated that various glands produced physiologically active secretions. It had been known, for example, since 1683 that removal of the pancreas produced diabetes-like symptoms in dogs. In 1889, Minkowski and von Mering described their well-known experiment relating pancreatic secretion with sugar metabolism. Berthold in the middle of the nineteenth century had shown that the effects of castration on comb growth of the rooster could be prevented by transplantation of testicular tissue. In the case of the thyroids it was shown in 1856 that mortality in dogs and guinea pigs caused by thyroidectomy could be prevented by thyroid transplants. Ten years before the turn of the century hypothyroidism in humans was successfully treated with thyroid tissue. Adrenal malfunction had been associated with the symptoms of weakness and pigmentation which we recognize as Addison's disease in 1849. The androgenic hormones of the testis had received great notoriety, particularly through the work of Brown-Sequard in 1889 who claimed powers of rejuvenation from testicular extracts. With the estrogens, similar experiments were carried out in which transplantation of ovarian tissue prevented the uterine atrophy which otherwise occurred. In examining reports of these early experiments one is struck by the great reluctance of the age to assign a new explanation to an observed effect, however much the logic of the situation seemed to call for it. The experiments with transplanted thyroid and testis and with pancreatic extracts seem now to demand an explanation on the basis of a physiologically active secretion—in other words, a hormone—but biologists did not give up their earlier interpretations easily. As Hoskins has described it: "Up to near the end of the last century nearly every expert looked to the influence of the nervous system alone as concerned with the coordination of functions in the body; the conception of chemical regulation had achieved no place in the mind of the majority."

What broke the spell was epinephrine. It was recognized as a potent pressor substance in 1894 and isolated as a benzoate by Abel in 1900. With Parke-Davis' active support it was crystallized by Takamine and by Aldrich in 1902. It was synthesized in 1904, and marketed shortly thereafter for the treatment of shock. This work was speedy, clear-cut, and medically useful. It demonstrated beyond a doubt that an endocrine gland could produce an exceedingly potent compound, (1 part per billion), that that compound could have useful applications, and that it could be synthesized in a standard manufacturing operation. The way was open for isolation of more new hormones.



Epinephrine

Accordingly some of the other portions of the endocrine system came in for a sharper scrutiny. The corpus luteum of the ovary was shown to be essential for maintenance of pregnancy in the rabbit, and the ground-work was thereby laid for Corner and Allen's demonstration twenty years later of progesterone. By 1905 the dominance of the Pavlovian theory of nervous control of phy-

siological function had been dissipated sufficiently so that one of its last strongholds could be invaded by the hormone concept. This territory involved the control of digestive function. It is appropriate that the word hormone was coined by the same physiologist who established the hormonal nature of secretin, the intestinal agent regulating the volume of pancreatic flow. Evidence for another of the gastro-intestinal hormones, gastrin, a pyloric substance which stimulates gastric secretion was brought forth by Edkins at almost the same time.

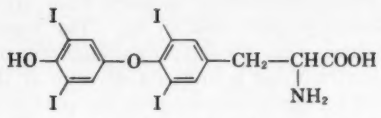
As well as marking the founding of the Medicinal Chemistry Division of the American Chemical Society, the years 1909–10 were significant ones in the unfolding of the hormone story. The pituitary began to come in for attention. Experiments involving its ablation had been carried out earlier and Minkowski had associated acromegaly (a chronic disease characterized by enlargement of the bones and soft parts of the hands, feet, and face) with pituitary hyperfunction, but the effect on growth was most clearly shown by Aschner in 1909 who produced dwarf dogs by hypophysectomy. Similarly, oxytocin, the posterior pituitary principle inducing contractions of the uterus was recognized by Dale a few years earlier. The stage was set for later study of the gonad-regulating hormones of the pituitary by the observation of loss of gonadal activity in similar dog preparations. The function of the parathyroid was identified before the close of the decade with McCallum and Voigtlin's discovery of the control by this gland of calcium levels in the blood. Finally 1909 was the year in which insulin received its name, although its existence was to remain hypothetical for almost another generation. The vigorous attack on physiology which began in the first decade of the century seems to exemplify more than anything else the breadth of progress which is made once a misconception has been replaced by a valid principle.

Insulin: Triumph of the 1920's

The high point of the following decade involved the thyroid. By the beginning of World War I, the thyroid was well enough understood that clinical treatment of myxedema with thyroid tissue was an established practice. Nevertheless it must have been a very exciting moment in the Mayo Clinic when E. C. Kendall first noted in the bottom of an evaporating flask the white crystalline crust which was the first thyroxine ever to be seen by man. The day was December 25, 1914.

The years of the 1920's are memorable not only for the chaotic social scene but also for the spectacular isolation of insulin and the conquest of diabetes. The discovery by Banting and Best in 1922 that the difficulty in the isolation of insulin could be gotten around by avoiding destruction by the enzyme trypsin led to rapid development of the field. The initial active extracts were purified by Collip to a degree where they were suitable for human injection. Eli Lilly, which had supported much of this work supplied almost a million dollars worth of free insulin for experimental investigation. Their confidence was justified when the clinical results began to come in. "Patients reeking of acetone, in heavy coma, in hopeless condition on delivery at hospital, a few steps away from the undertaker, were saved."

The 20's also saw further progress on the thyroid. Twelve years after Kendall's isolation of thyroxine, Harrington determined its structure and synthesized it.



Thyroxine

Work on the pituitary went on. Growth hormone was brought to wide public attention by the giant rats produced in Evans and Long's laboratory at the University of California. At the same time pituitary extracts with thyrotropic and luteinizing activity were prepared. The function of the posterior pituitary was partially clarified in 1929 when Verney discovered that the power of the kidney to concentrate urine was regulated by posterior pituitary extracts. In the absence of this secretion which we now know contains the hormone vasopressin, the kidney failed to reabsorb water, and a condition equivalent to diabetes insipidus developed. Still other pituitary hormones were beginning their biological characterization in the 1920's. The adrenocorticotrophic hormone, ACTH, was investigated in the form of crude pituitary extracts by several groups.

The Gains of the 1930's: Chemical Syntheses

Many of the problems which had their biological inception during the early years of the century began to reach their chemical fruition in the 30's. The chemist was now needed to make his contribution where the biologists left off. The isolation and crystallization of the steroid hormones esterone, testosterone, and progesterone were all carried out in the depression years of the early thirties. They were no sooner isolated and structurally deciphered than they were synthesized. In fact so eager were the chemists at long last to contribute their synthetic skills that they sometimes synthesized hormones before they could be isolated as was true with estradiol for example. No sooner were the hormones synthesized than analogues were made with superior properties such as methyl testosterone, ethisterone, and diethylstilbestrol. The pharmaceutical industry, which had had little chance to contribute since the advent of insulin, began to feel useful again. Outstanding pioneers in the synthetic steroid hormones of this era were the European-based companies Ciba, Roche-Organon, and Schering, A. G.

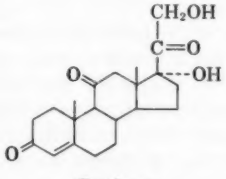
At exactly the same time the adrenal cortex was being resurrected from the discard where—unbelievably!—it had been consigned following the brilliant but distracting chapter on epinephrine and the investigation of the adrenal medulla. Even as late as 1929 there were still many apparently who held that epinephrine could account for all of the physiological effects of the adrenal. There were several laboratories, however, where it was held that only part of the adrenal story had been told. One was that of Professor Wilbur Swingle in Princeton where biologically-active extracts of beef adrenals were prepared. Following purification of active extracts, isolation and structure determination went on smoothly. Three

laboratories contributed, one in Rochester led by E. C. Kendall, one at Columbia with Wintersteiner and Pfiffner, and one in Basel with Reichstein. The adrenal cortical hormones turned out to be structurally more complicated than those of the sex hormones and since Addison's disease was adequately taken care of by adrenal extracts plus desoxycorticosterone, and since further there was no other medical application on the horizon, no one struggled to synthesize them. There the matter rested until nearly five years later.

The fourth decade of the century also included advances in the problems of intestinal hormones. The study of the complicated responses of the stomach, the gall bladder, the pancreas, and the intestine to the ingestion of food had been initiated in the early 1900's as noted earlier. During the 30's Ivy and others clarified the tangled picture by providing more evidence for the existence of secretin and gastrin and adding to these, four additional humoral agents having to do with digestion. They were all short-acting polypeptides or proteins which are still not fully characterized chemically. One was cholecystokinin, a gall bladder-stimulating substance in the intestine; pancreozymin, a hormone causing secretion of pancreatic enzymes; enterogastrone, a hormone inhibiting gastric activity and secretion; and urogastrone, a highly potent organic base appearing in urine and which had anti-ulcer properties under specified conditions. Because of the fact that none of these hormones is characterized by a deficiency disease so far as is now known, and also because extripation of the cells producing these hormones entails loss of the small intestine, experimental studies which might link them with human pathology have made slow progress. It is at this stage that we shall leave the gastro-intestinal hormones and turn back to the dramatic events of the 1940's.

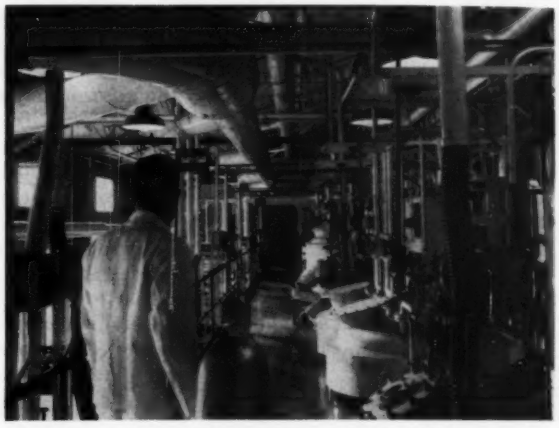
Breakthrough of the 1940's: Cortisone

The fifth decade of the century was marked by the major medical breakthrough of the discovery of the anti-inflammatory action of cortisone. As with any such development, a great deal of preparation had gone into setting the stage. The synthesis of adrenal steroids



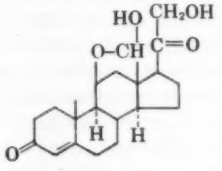
Cortisone

was a wartime project from 1941 to 1944, cloaked in secrecy and enlivened with false rumors. In reconstructing this period I am a little hampered for lack of perspective from the organizational levels responsible for deciding that the adrenal steroids were a promising bet as agents for military medicine. My position was that of an organic chemist, fresh from Professor Wallis's laboratory in Princeton, assigned the job of synthesizing cortisone. This I was fortunately able to do with the aid of a timely reaction discovered by Reichstein in Basel. In retrospect however one of the absolutely essential contributions to the discovery of cortisone was the conviction of E. C. Kendall and of R. T. Major, then Director of Research of the Merck Laboratories, that cortisone had to be good for something. It is just barely conceivable that even now, ten years later, no one would have taken the hundred-thousand dollar gamble to get cortisone into clinical studies.



Fine chemical manufacturing installations at the Upjohn Company perform part of the production of finished steroid hormones.

Discovery of the last of the steroid hormones, aldosterone, came as a natural outgrowth of the earlier work on adrenal extracts. Success had to be delayed however because aldosterone is present in less than 1 per cent of the abundance of hydrocortisone in the adrenal and is very much more sensitive to chemical reagents. With the application of paper chromatographic techniques and of an exquisitely sensitive assay using radioactive sodium and potassium, Tait and Simpson successfully purified concentrates of aldosterone in 1951. Crystallization, structure, and total synthesis followed in a collaborative effort with the Ciba Laboratories in Basel.



Aldosterone

The existence of aldosterone has occasioned the discovery of the newest of the endocrine diseases, Conn's syndrome or primary aldosteronism. The condition is characterized by excessive secretion of aldosterone and has an incidence of 300 known cases in the approximately 2,000,000 world population.

1950's: Progress on Peptides

As the present decade closes, it seems that future historians of biological chemistry will recognize it as the golden age of the peptide hormones. The biological and medical groundwork which had been so painfully worked out during the first half of the century provided a perfect challenge for the peptide chemist. The challenge was, first, one of structural identification; second, of synthesis. The pioneering work of Sanger on insulin was begun at Cambridge in 1943 and brought to a suc-

cessful conclusion twelve years later. When the work was started the gross composition of insulin in terms of its amino acids was known, but its true molecular weight which is 6000, was not. Due to association in solution erroneous figures as high as 36,000–48,000 were given. Can you imagine the degree of optimism which was necessary in 1943 to embark on the proof of structure of a compound with a molecular weight of this magnitude! One other incredible fact which has been pointed out by Sanger serves to show how rapidly the field has moved. When the insulin work was begun there was only one protein in which the position of an amino acid residue had been identified. This was insulin, in which phenylalanine was known to be an N-terminal group. For the insulin work new techniques had to be invented in order to make progress on the structure. These included the technique of partial degradation to overlapping peptides and the application of paper-chromatograms to separate the degraded fragments, the use of 2,4-dinitrofluorobenzene to identify N-terminal residues, and location of disulfide cross-links by performic acid oxidation to cysteic acid-containing peptides.

So successful was the progress of the Cambridge group that the other polypeptide hormones came in for prompt attention during the early 1950's. Adrenocorticotropic hormone had been isolated from beef pituitary by Li's group at California in 1943. With the recognition of cortisone as an anti-inflammatory agent it was brought to clinical trial and proved—apart from the inconvenience of parenteral administration—to be equivalent therapeutically. In 1949–50 the Armour Company put the purified beef ACTH in the hands of clinicians.

The problem of absolute homogeneity of polypeptides especially from natural sources has undoubtedly been one of the most vexatious to face biochemists in the last decade. The discovery that crystalline insulin harbored glucagon, in addition to an insulin analogue differing by one NH_2 group stimulated study on both new techniques of purification and on new criteria of purity. The adrenocorticotrophic hormones, the melanocyte-stimulating hormones, growth hormone, the vasopressin-oxytocin mixture—all were fractionated and refractionated through the use of partition chromatography, countercurrent distribution, an ever-widening spectrum of ion-exchangers, zone electrophoresis, and paper chromatography. When a product had been purified to the stage of homogeneity by both biological and physical criteria, it was submitted to gross amino acid analysis and then partial degradation and sequential analysis. So efficient has this procedure become that only 12 mg was required to decipher β-melanocyte-stimulating hormone. Contrary to the rather pessimistic view that each polypeptide might have to be represented by a statistical distribution of amino acid residues, it has turned out that each polypeptide hormone which is pure by the best available physical criteria represents a unique sequence of amino acid residues. Or, to look at it the other way, present techniques for purification of the polypeptides are sufficiently delicate to separate individual components differing in only one or two amino acid residues.

Using these ultra pure samples and applying the methods successfully used with insulin, the amino acid sequence of five classes of polypeptide hormones has been worked out over the last few years. Within each biological class a slight amount of variation with species has been found. The MSH's and ACTH's are the most throughly studied and there it has been found that hog, sheep, and beef ACTH differ from each other in four to six amino acid residues in the 25th through 33rd positions in the chain. Similarly the difference between β-MSH of swine and that of cattle consists of the replacement of one amino acid residue by another (glutamic for serine).

The species specificity of these slight structural variants has provided an area of great theoretical interest and some degree of practical interest as well. The various ACTH's all appear to be active in different warm-blooded vertebrates. The receptor sites for growth hormone on the other hand are more specific so that a preparation active in man can be apparently obtained only from primates and not from more commercially available sources.

Not only do several structural variants of a polypeptide hormone like ACTH show the same qualitative physiological response, but a single structure can show more than one hormone response. We are familiar with this phenomenon in the case of the adrenal steroids where aldosterone shows both glucocorticoid and electrolyte-regulating effects. Among the polypeptide hormones the vasopressin-oxytocin duo is a conspicuous example. Biological crossover of this sort occurs with MSH and ACTH as well. When these hormones are isolated from natural sources there had been constant apprehension that biological duality might be due to contamination with small amounts of another active hormone. It has been one of the great contributions of the organic chemist in the last few years to synthesize samples of oxytocin, vasopressin, and most recently of α-MSH which are completely free of their naturally occurring biological contaminants. The groups of DuVigneaud, Boissonas, and Hoffmann have thus been able to settle in a clear way the fact that there are dual responses from these pure chemical entities.

A Sampling of Present and Future Problems

This brings us to the present moment in hormone research. I shall not attempt to make predictions about the results to be expected in the decade to come. Rather let me briefly itemize a sampling of problems of current interest which may serve as indicators of tomorrow's results. In the way of hormones which are still inadequately characterized or isolated, the hypothalamus seems the most promising territory. The regulation of the anterior pituitary by humoral agents stemming from the hypothalamus is exemplified by CRF, the corticotrophin-releasing factor of Saffran and Schally and of Guillemin. The latter is active at fractions of a microgram and appears to be a peptide. Sayers' lipid-soluble hormone from the pineal which controls release of aldosterone will make a fascinating study when its structure is elucidated. Will it be easier to devise antagonists to it than to aldosterone itself? On the synthetic front glucagon and ACTH seem conquerable; attacks are underway in at least two laboratories. The structure of growth hormone will no doubt be

achieved, but it is so much larger than ACTH that it can hardly be expected soon.

The relating of the physiological activity of the protein and polypeptide hormones to their structure hangs on methods for determining the essential functional groups and then determination of the architecture of the active sites. As an example of a first step in this direction, X-ray crystallography has provided a satisfactory three-dimensional model of insulin. The presence of a left-handed α-helix up to the disulfide bridge in chain A followed by a right-handed helix in the remainder of the molecule represents a model with at least the architectural significance of the Watson-Crick DNA molecule or the conformational representation of the triterpenes. What can be done with the model will be a fascinating problem.

Finally, there ought to be mentioned the phase of hormone research which is always one of the last to be solved. That is, of course, the mechanism of action at the molecular level. The problem has been struggled with during most of the 50 years of the medicinal chemistry division's existence. The experiments of Haines relating the acceleration of synthesis of adrenal steroids with ACTH via reduced triphosphopyridine nucleotide provide a good example. The attempts to pin down the mechanism of action of insulin to glucose transport across the cell wall and the speculations on estrogens as accelerators of pyridine nucleotide transhydrogenase break into new territory. Undoubtedly the problem of mechanism will be one of the most fertile of biochemical areas for many years to come.

Sidney Udenfriend
National Institutes of Health
Bethesda, Maryland

The Role of the Biochemist in the Search for New Therapeutic Agents

Natural products and their extracts were already in use as therapeutic agents when recorded history began. Many of these ancient remedies are in use even today, in modified form. However, the application of some degree of rational approach to the development of therapeutic agents began with the introduction of organic chemistry and modern biology, bacteriology, parasitology, physiology, etc. Organic chemists isolated active compounds from natural products, determined their structures and, as they improved their techniques, they synthesized related compounds with even greater activity. Biologists became more sophisticated, too, and as clinicians became more experimental, scores of valuable therapeutic agents were introduced: anaesthetics, analgesics, vaccines, antibacterial agents, antipyretics. All these were introduced successfully long before the advent of modern biochemistry. At the present time the team of organic chemist, biologist, and clinician still produces new agents at a rate which, if anything, is increasing. Reserpine, thorazine, imipramine, and diurel are but a few examples of the continuing success of this approach. However, even with these notable successes most of us still feel that there will eventually be a more rational way to approach the problem of developing new therapeutic agents.

One of the first suggestions that therapy might benefit from a biochemical approach followed the introduction of sulfonamides and the demonstration of the growth requirements for the related compound, *p*-aminobenzoic acid. As it became apparent that the structural relationship between these two could have something to do with the antibacterial activity, the notion of antimetabolites, as therapeutic agents, was introduced. This concept has already helped in our understanding of drug action. However, the major limitation to a more successful application of antimetabolites to therapy has been our meager understanding of the biochemical and physiological mechanisms of the metabolites themselves.

As biochemistry continues to make progress in explaining the mechanisms of living processes, it becomes apparent that it provides a wealth of information which it should be possible to put to use in the development of therapeutic agents. Each new enzyme and each new metabolic route is potentially capable of leading to some advance in therapy.

At the recent meetings of the Pharmacology Society in Miami, it became apparent that large strides are being made in providing biochemical answers to a variety of therapeutic problems. Strominger reported on the effects of penicillin and other antibiotics on the synthesis of bacterial cell wall. This work combines the most fundamental with the most practical in bacteriological research. Sutherland and Rall reported on the relationship of the effects of epinephrine and glucagon to a new metabolite, cyclic adenylic acid. These and many other exciting facts were reported at the teaching seminar, all of them presenting some biochemical findings relating to physiological action or therapy. The tenor of these meetings indicates that biochemistry, without question, has found a place in the quest for therapeutic agents. *The problem is, where does the biochemist fit in in the team of organic chemist, biologist, and clinician which is already functioning with reasonable success?*

Biochemistry is an immense science concerning itself

Presented as part of the 50th Anniversary Symposium, Division of Medicinal Chemistry, American Chemical Society, September 16, 1959, Atlantic City, New Jersey.

with all matters relating chemistry to life processes. It is apparent that advances in the remotest areas have far-reaching implications, many of which may contribute directly or indirectly to therapy. However, I would like to limit my discussion to the *direct* applications of biochemistry to therapy. These include: (1) Attempts to explain the actions of older drugs; (2) Help in setting up of proper regimens for existing drugs; explanations of toxicity, etc.; (3) Attempts to develop new therapeutic agents.

I will be the first to admit that biochemistry has yet to offer a completely rational explanation for the actions of any existing drug. However, our knowledge is still only fragmentary and every day new biochemical processes and principles are uncovered which contribute important leads. In this area we have suffered many disappointments. However, these have taught us valuable lessons too. Thus, the demonstration that anaesthetics and analgesics, *in vitro*, can uncouple oxidative phosphorylation appeared significant to an earlier, more naïve, biochemistry. Now we realize that such a theory contributed little to our fundamental understanding and to the practical development of improved anaesthetics. While our findings in this area were negative they taught us to look for more selective mechanisms and specific sites to explain the actions of such specific agents. We also know now that biochemical effects demonstrated, *in vitro*, must be duplicated *in vivo* at dosages which are in the therapeutic range, in order to be meaningful. Obviously reliable information concerning the mode of action of a well-known drug can lead to the development of newer ones. If it inhibits a certain enzyme, other inhibitors can be tried. If it releases certain hormonal agents, related compounds may be more active or less toxic. These can all be followed by screening with relatively simple biochemical methods.

The second important aspect of biochemistry concerns the application of analytical procedures to make sure that agents with certain therapeutic potential are used properly. Are they absorbed through the gut? Do they penetrate into the pertinent tissues when administered in a given dose via a given route? More important, does a drug developed to produce a given biochemical effect actually produce *that effect* in patients, in the dosages employed for therapy. Information of this type must be channeled back before further progress can be made in our understanding of drug action or in the development of new agents.

I would like to give as an example the current use of monoamine oxidase (MAO) inhibitors. These agents were first used experimentally for the treatment of mental disorders because they were known to influence amine metabolism in the central nervous system of animals. Although this is of great interest it itself does not provide fundamental knowledge since we do not as yet know how the amines themselves act. However, screening for such activity *in vitro* and *in vivo* has brought forth many more compounds with similar activity. Now even though these compounds were introduced over two years ago it is only recently that methods are being developed to determine whether these agents do indeed inhibit MAO in patients and to what extent. I have heard many individuals, some in important positions in academic research and pharmaceutical industry, state that they doubted that the therapeutic actions of these drugs were due to this specific biochemical effect. Now there is something wrong with such reasoning. If there is no connection, why the very elaborate and expensive screening and synthetic programs? If, on the other hand, there is a direct relationship, why not invest sufficient time and money to *establish this beyond doubt?*

The third area where biochemistry can contribute is the most speculative but the most exciting; that is in the development of entirely new types of therapeutic agents.

Before I go into this I would like to point out that none of the sciences today is capable of *predicting* the therapeutic effects which may result from a particular manipulation of a biological system. As biochemists all we can hope to do is to modify specific biochemical reactions in the hope that we will obtain a physiologic response *in vivo* dependent on the activation or inactivation of that specific site. However, the exact nature of the over-all *in vivo* response of such a new specific reagent is unpredictable and its therapeutic applications even more so. Nevertheless, biochemists can point to many areas and say that chemical manipulation here or there can lead to *interesting* compounds. If one in ten of these turns out to be a useful drug I would consider this an excellent achievement.

Where does the biochemist turn for his leads? To chemical steps in the formation of substances specific for given tissues, organs, or chemical processes. Examples of these would by γ-aminobutyric acid (GABA) in brain; hydroxyproline in connective tissue; chemical steps in parasite metabolism; specific transport mechanisms of various metabolites into different cells; storage and release mechanisms of hormones and related humoral agents; chemical steps in inactivation of physiologically active agents; isolation and determination of substances from nervous tissue, eye pigments, etc. All these should be amenable to the influences of specific chemical agents and could lead to interesting pharmacological effects. Some of these chemical agents could even turn out to be therapeutically active.

Now it must be apparent to most of you that I have dealt with biochemical contributions and advances in rather general terms. I could go into specific examples from our own work and that of others. However, I would like to take this opportunity to discuss the role of the biochemist within pharmaceutical industry. Biochemists in academic laboratories have benefited greatly from pharmaceutical industry both directly and indirectly, through fellowships, grants, gifts of chemicals, consultantships, collaborations, etc. In that respect chemical and pharmaceutical industry have been invaluable to the biochemist. However, what of the practice of biochemistry within industry? What about the biochemist who finds himself within industry? In connection with this matter, see table which follows. As you can see, in the first quarter of 1957 and 1958 industrial organic chemists and pharmacologists accounted for 1 in 5 papers in their respective professional journals. The *Journal of the American Chemical Society* has similar values. However, only 1 in 300 was published in the *Journal of Biological Chemistry*, and that one was in collaboration with a university group.

Publications by Scientists in Chemical and Pharmaceutical Industry

Journal	January, February, March 1957	1958	Total	% of Total
J. Organic Chemistry	48/261	37/206	85/467	18
J. Pharmacol. and Exp. Therap.	9/38	4/36	13/74	18
J. Biological Chemistry	0/146	1/158	1/304	0.3
Archives of Biochemistry and Biophysics	4/90	7/87	11/177	6

In the *Archives of Biochemistry and Biophysics* industry published 1 in 17. Half of these concerned analytical methods.

What is the significance of this? To me it indicates that at a time when the biochemist is making great strides in mechanisms of living processes chemical and pharmaceutical industry are not making *direct use* of his talents as a biochemist. The limited publications in the biochemical journals indicate a number of things: Relatively few biochemists are employed by industry. Many who are called such are in effect organic chemists. Those biochemists who are in industry *cannot* or *do not* pursue lines of research resulting in papers acceptable by their professional journals. By contrast organic chemists and pharmacologists can do so readily.

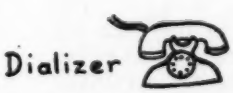
The impression I have of much of research in pharmaceutical industry is that it still adheres to the principle of leadership by organic chemists and pharmacologists and that these two utilize the biochemist in a service capacity. Thus, the biochemist may be told: "We have a new compound; develop a method for assay. How is this given compound metabolized? What enzyme does *our* new drug affect?"

Obviously these are necessary services which a biochemistry laboratory in industry should supply. They are bread and butter functions, but the biochemist cannot survive as a scientist on bread and butter alone. If he is to flourish as a distinct member of the research team, he should be permitted to explore biochemical leads on his own, and to make suggestions to the organic chemists and pharmacologists in turn. There is no reason why a biochemistry laboratory in industry should not be able to conduct research which is at one and the same time intellectually stimulating and also of potential value in developing new therapeutic agents.

With all the interest in drugs which can influence monoamine oxidase, catechol methylpherase, and amino acid decarboxylases, why shouldn't biochemists in industry work on purifying these enzymes? It is certainly possible that identification of the cofactor of MAO could lead to a better understanding of how MAO inhibitors work and therefore to new agents. In any event isn't it desirable to have members on the staff who know more about the problem than the mere bioassay procedure involved in screening? The biochemistry of the bacterial cell wall would also be an excellent and timely study leading to many fundamental and practical things.

Too frequently the industrial biochemist is permitted only to pursue the screening portion of a research problem and leave the most exciting portions for others. This can be quite frustrating. Alternatively his talents may be used for more biological or chemical programs. I don't believe that it is a luxury to permit biochemists to carry on stimulating *biochemical* research programs. One can point to many departments outside industry from which numerous practical contributions continue to come year after year. Would not such departments be just as useful within an industrial framework? I believe they would. However, careful examination reveals that a biochemistry laboratory to be able to function so that it can satisfy both the research requirements and day to day developmental studies would have to be much larger than any in industry today. I believe that there is a critical size of a laboratory below which a company cannot make proper use of a biochemical group even if it so desires. Increasing the professional and technical manpower of a biochemical laboratory beyond a certain point increases the thinking and research potential far in excess of the mere number of individuals hired. I believe that in its initial overtures to biochemistry industry is doing what appears to be sensible; that is, building up the size of laboratories slowly as one would do in any experimental venture. However, I think that this is a serious error. I firmly believe that the first company which decides to build a department of biochemistry in the same manner as is done in a university or research institute will find itself in a very favorable position. What I mean by this is not only the setting up of a department under the direction of an outstanding investigator but the understanding that he will be permitted to select a staff of his own choosing and to participate in those areas of research which are of interest to him and his colleagues. The contributions from such a department to the company should then be measured not in the number of products but in the number of interesting findings of biological or pharmacological significance. With a sufficient number of these findings the organic chemist, biologist, and clinician should be able to *increase significantly* their rate of development of new therapeutic agents.

Chem Gems



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C. Jelleff Carr
National Institutes of Health
Bethesda, Maryland

The Contributions of Medicinal Chemistry to Psychopharmacology

Imperishable monuments that bespeak the success of the medicinal chemist surround us, and we need no signposts to find his memorial on this Golden Anniversary occasion. The fact that the history of medicinal chemistry is impressed upon the practice of medicine in 1959 illustrates the magnitude and scope of his skillful performance for the past 50 years. Indeed, the very brief history of my subject of psychopharmacology stands as a triumphant example of his most recent achievements. To understand why the discovery of psychoactive drugs made such a profound impression upon medical practice, one must look at the history of our knowledge of the chemistry of the brain. From this historical background we can draw numerous significant conclusions.

Dr. Irving Page has pointed out that while the chemistry of biology in general, and the chemistry of the human body in particular, were becoming well established in the past 50 years, the chemistry of the brain was ignored and remained in formidable isolation. The task of analyzing brain function in terms of chemical changes must have appeared too great an undertaking to many chemists. Thirty years ago neurochemistry was referred to as the chemistry of "brain hash" and was unappealing as an area for chemical study. It seems that neuronal transmission of the nerve impulse intrigued the electrochemist, and the foundations for neurophysiology in terms of electrical activity were laid prior to the formulation of corresponding ideas of chemical changes. There was a strange early preoccupation with the analogy between the movement of an electric current over a wire and nerve transmission. Only later were the chemical theories of nerve transmission evolved.

One cannot deny that modern electrical techniques have given us a remarkable degree of understanding of the functions of the central nervous system and behavior changes. In the last 10 years the work of Hess, Sheer, Jasper, and Delgado, to mention only a few significant contributors, has made it possible to record behaviorally-evoked electrical activity from various brain areas and to transmit electrical stimuli into the brain of conscious animals or humans. We now know that electrical stimulation of specific brain areas via microscopic electrodes can produce coordinated muscle movements, hallucinations, and emotions of hostility and friendliness, and such stimulation has been shown to modify human thoughts. The results of such stereotaxic mapping of the brain are providing an understanding of behavioral neuroanatomy that is unique and provocative. However, eventually are not these electrical effects at the neuronal, cellular level, chemical? It seems most appropriate to search for the chemical changes that are induced by electrical stimulation; perhaps these same changes can be evoked and controlled by drug administration more reliably.

When we look back and realize that Hunt isolated and studied acetylcholine in 1911, and in 1900 Abel separated epinephrine, it seems a bit incredible that it was as recent as 1921 when Loewi first demonstrated the significance of acetylcholine as a parasympathetic neurohormone and about the same time Cannon identified epinephrine as the chemical mediator liberated by sympathetic nerve impulses. Even with these discoveries the concept of chemical transmission of nerve impulses developed slowly, and the idea of chemical interaction within the central nervous system was essentially ignored.

Remarkable, too, in the light of our present knowledge is the late discovery of norepinephrine in adrenal extracts. Holtz and his associates in 1942 found that the suprarenal glands elaborate norepinephrine as well as epinephrine and subsequently it was shown that USP standard epinephrine samples contained from 10 to 18 per cent norepinephrine. It is striking that this high percentage of norepinephrine in adrenal extracts should have remained undetected for nearly forty years. This is significant when one considers the recent discovery of norepinephrine in the brain in appeciable amounts. It is proposed that norepinephrine serves as a neurotransmitter in the so-called ergotrophic system of the subcortex. Here its action encourages activity and wakefulness. Since epinephrine and norepinephrine appear to be intimately related to nervous system functioning, numerous investigators are exploring the biochemistry of these hormones within the central nervous system. With this lesson from history, we may ask, what other chemical compounds are we overlooking in our study of the nervous system?

There is an extensive though controversial literature on abnormal epinephrine metabolic products and their association with schizophrenia. I refer to adrenochrome, adrenolutin, and their possible psychosis-inducing effects. However, these concepts may be premature, for only within the past year, as a result of the studies of Axelrod and associates, has the determination been made of the principal metabolic pathway of epinephrine. The enzyme catechol-ortho-methyl transferase has been identified and implicated as the enzyme mainly involved in terminating the action of epinephrine. The enzyme monoamine oxidase apparently plays a secondary role mainly in deamination of the metanephrine formed from ortho methylation. These studies provide a clearer picture of the metabolic

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chemistry of this neurohormone and illustrate how recent and fragmentary our knowledge is of this important neurotransmitter.

In the years preceding the recognition of the psychoactive drugs many compounds were discovered that should have suggested to pharmacologists the idea that thinking can be influenced by chemicals introduced into the body. Through the years substances of known composition were reported that produced abnormal behavior effects in animals and man. The reports of explorers in the little-known regions of the world, the studies of anthropologists and psychologists on the mores and behavior of primitive peoples, and the careful scientific evaluations of the effects of plant and animal drugs on man and animals, indicated that hallucinations, changes in thought, mood, and perception can be caused by substances that are eaten, snuffed, chewed, or inhaled.

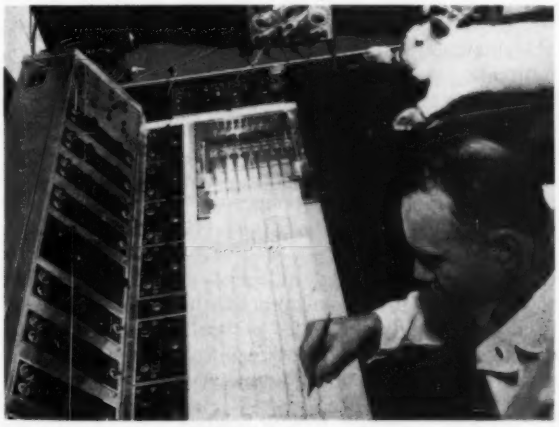
We have known morphine for 150 years, and we are well aware of the behavioral changes induced in addicts by the opiates and the synthetic analgesic narcotics. These are potent drugs that produce disorientation, memory disturbances, and stupor. The hydantoins and related anticonvulsive agents with their selective action on the motor cortex might have suggested that other chemicals would antagonize the turbulent, aggressive, destructive states of chronic psychotics. However, this was not to be, and we had to wait until the stage was properly set for the persuasive actors, LSD, reserpine, and chlorpromazine to appear from Switzerland, India, and France.

Discovery of Psychotomimetic Agents

The concepts of chemical psychosis and therapeutic behavioral changes induced by drugs were not born naturally. However, in retrospect, it is difficult to understand how the idea could have been denied so long. I must admit that even though for years I looked at animals and men under the influence of many chemical substances, it never once occurred to me that any of these drugs might be used to influence therapeutically abnormal mental function in man. In fact, I was exceedingly skeptical of the potential value of drugs like amphetamine to improve mental performance, although the obverse, namely deteriorated performance caused by drugs, was acknowledged. In this public confession I take some comfort from the realization that I have numerous and distinguished company. I believe the view was generally held that drugs were essentially deleterious to good brain function and that if any effect at all was produced, it was one that would decrease mental performance and give rise to undesirable behavioral changes. It was from this unfavorable pharmacologic milieu then, that the phenothiazine and rauwolfia drugs emerged.

The almost simultaneous reports of the remarkable effects of minute amounts of lysergic acid diethylamide accidently discovered by Hofmann, and the effects of chlorpromazine and reserpine in tranquilizing states of agitation and anxiety in mental illness, were two factors that catalyzed the explosive growth of psychopharmacology since 1954.

Hofmann in 1943 while synthesizing derivatives of lysergic acid inadvertently absorbed a microscopic quantity of LSD. The alterations in perception, free play of imagination, bodily sensations of changed shape with an uninterrupted stream of fantastic images of extraordinary vividness, accompanied by an intense, kaleidoscopic play of colors, led him to the deliberate ingestion of 250 micrograms. The mental effects were repeated, and it was observed that amounts orally as small as 0.5 to 1.0 microgram per kilogram would produce these results rather consistently. This discovery was disclosed in 1947 ,and it provided a potent stimulus for exploration of related substances. A recent tabulation disclosed that 15 chemical compounds of known structure have been reported to elicit psychotomimetic effects in man. It is of considerable interest that of the 18 derivatives closely related to LSD synthesized by Stoll, Troxler, and Hofmann, only two induced marked psychotic-like changes in man.



In the Abbott Laboratories, the electroencephalograph provides additional data on drugs such as anticonvulsants and tranquilizers.

The significance of the discovery of psychotomimetic agents is related to two facts: one, the demonstration that specific chemicals can induce in man thinking disturbances, and two, the possible role metabolic biochemical lesions involving the endogenous formation of psychotogens may play in mental illness. In the first case these compounds become candidates as incapitating agents for chemical warfare, and in the second instance their discovery may indicate that indeed some forms of mental aberration may be the result of modified brain chemistry. It was this latter hypothesis that led to the Symposium on the Chemical Concepts of Psychosis held at the Second International Congress of Psychiatry in Zurich, in 1957.

Reinforced by the discovery of so many drugs useful in mental illness, illustrious scientists from many disciplines throughout the world are focusing their attention on the recent advances in chemistry as these are related to psychiatric states. Truly, this is a changed outlook from psychoanalysis or mere custodial care of only a few years ago. Today chemical mechanisms of the brain are no longer to be denied and the future is bright for the ultimate synthesis of curative drugs and certainly for a better understanding of the workings of the central nervous system.

As soon as it had been shown that chlorpromazine and reserpine were capable of controlling hyperactivity

and disturbed behavior in psychotic patients, the way was opened for the medicinal chemist to make his contribution. This is an old story, the fitting of substituent groupings to the kind of drug effect desired. However, a new problem arose. What is the desired effect and how is it measured? If a mental patient is "improved," in what ways is he improved and how can we assess his degree of improvement? In infections the disappearance of the invading organism, the drop in body temperature, and the healing of the wound are objective measures of drug therapy. In diabetes following insulin or anti-diabetic drug administration the blood sugar level returns to normal, ketonuria disappears, and the patient gains weight lost in illness. In a similar fashion, most of the organic diseases have a symptomatology readily enough identified by patient and physician alike, so that remission of symptoms or cure is unmistakable. This is not so of mental illness involving behavior changes. The psychotic subject has a labile behavior, changing in an unpredictable manner that is influenced by his surroundings, both physical and social. If a drug is administered it is extremely difficult to determine whether or not any change that follows, either desirable or undesirable, is the result of drug action. For this reason it has been known for a long time that almost any form of treatment will be liable to produce some kind of behavior change in the mentally ill. It was this knowledge that tempered the enthusiasm of the early workers with tranquilizer drugs. Indeed, today we are just coming to the stage of drug development when we can say as a result of properly controlled clinical studies that some of the more active phenothiazines do in fact act as palliatives as long as drug administration is continued.

Psychopharmacology, a New Science

This brings us to a definition of psychopharmacology. Psychopharmacology, from the viewpoint of the pharmacologist, represents an area of pharmacology dealing with those chemical substances that selectively affect behavior in animals and man. Obviously those chemical compounds that produce behavioral effects that can be applied to salutary ends in mental illness are the most valuable psychopharmacologic agents. One might exclude from this classification the anesthetics, the narcotics, and the hypnotics as drugs that are of only incidental value in mental illness. Drugs are not classed as psychopharmacologic agents if they only occasionally produce behavior changes in certain patients. Thus, cortisone in adequate doses may elicit in some individuals symptoms of euphoria or schizoid reactions. These effects are considered side reactions and until the drug action can be applied to therapeutic goals the drug is not a useful psychopharmacologic agent. On the other hand, the agents that produce bizarre behavior patterns or some modification of normal behavior in animals and man, the "hallucinogens" or "psychotomimetics" have found little place in therapy.

A pharmacologist at Smith, Kline and French observes the effect of a chemical compound on a conditioned response in a white rat.

Psychopharmacology involves scientists in four major disciplines—the organic medicinal chemist (for synthesis of chemical compounds), the animal psychologist (for assessment of behavior characteristics), the pharmacologist (for studies involving the mechanism of action, patterns of excretion and metabolism, and toxicity), and the psychiatrist and experimental clinical psychologist (for eventual clinical evaluation).

To state the scope of psychopharmacology in terms of these disciplines alone is misleading. Those drugs that have been most useful selectively change the behavior pattern of mental patients in such a way that they are said to be "improved." As I have mentioned, there is much difficulty in evaluating patients at a diagnostic level and in assessing their behavior and improvement. These clinical problems are as knotty as the bioassay of drug behavior effects using animal screening techniques. The quantitative measurement of behavior in man and in animals as influenced by drugs, is the *summum bonum* of psychopharmacology. Thus the advent of behavior-changing drugs created novel problems in pharmacology, and the future development of psychopharmacology is intimately tied to the measurement of behavior itself. Obviously this concept vastly broadens the scope of pharmacology from the enzyme, cellular, tissue, or organ level to the behavior of the total organism. As mental disease or the state induced by psychotomimetic agents is essentially a disorder of the brain as an information-carrying organ, a simile can be drawn to a maladjusted information-carrying system. If it is agreed that drugs can favorably modify these disorders then psychopharmacology may indeed embrace within the checkered pattern of its scope cybernetic speculation. According to such a concept traditional neuropharmacologic studies must be enlarged to include information theory and the psychopharmacology of behavior.

Psychopharmacology, then, is concerned with those drugs that regularly influence behavior of an organism. It embraces in addition to the traditional areas of pharmacology, the psychodynamic measurement of drug effects upon normal mental function and upon abnormal mental states. It may be restricted in a therapeutic sense to the action of those chemical agents that produce desirable behavioral effects in mental illness.

This infant science of psychopharmacology increas-

ingly nurtured by its related disciplines, especially medicinal chemistry, has produced a formidable group of drugs. There are 12 major tranquilizing-type drugs including the phenothiazines and reserpine alkaloids in clinical use. We have at least nine less potent drugs, phenothiazines, diphenylmethane derivatives, and substituted diols. Not including such central nervous stimulants as caffeine and Metrazol, there is a group of 13 antidepressive agents of miscellaneous structure including the recently introduced monoamine oxidase inhibitors. There are five non-hypnotic centrally-acting skeletal muscle relaxants available for use in anxiety-tension states, not to mention eight nonbarbiturate sedatives of miscellaneous nature.

Certainly medicinal chemistry has given us an abundant yield of drugs. However, valiant efforts will be required to understand the mental effects of these agents, to use them appropriately in mental illness, and to guide the development of the host of new compounds that are under investigation.

By now it is obvious that the drugs we possess do not exert a true curative effect in mental illness. They are palliative in the treatment of disturbed behavior and neurotic and psychosomatic reactions. The antidepressive drugs appear to be clinically useful in some types of depression; however, many patients do not respond to this therapy. For example, it has been recently recognized that some diagnostically differentiated depressed patients will respond most favorably to antidepressive drug therapy, while others will do best after electro-shock treatments. Thus the appreciation of the scope and limits of drug therapy will improve the percentage of successful results.

It may be possible to couple our growing knowledge of the chemistry of the brain with the design of chemical compounds that will selectively influence the abnormal mental state in a constant manner. Can we not reduce the "wide range" of effects of the currently-used tranquilizers to "narrow range" drugs influencing specific kinds of mental disease? This may be a matter of diagnostic importance; indeed, patient responsiveness to some drugs has already been pointed to as a diagnostic criterion. Obviously, improved drug therapy will parallel advanced techniques of diagnosis—the two are complimentary. I believe some drugs will be found that will cure, and that they will have a true psychotherapeutic effect. I think we will learn how the brain can be influenced by chemicals and how the brain exerts its own influence. I believe that there is being born a chemotherapy of mental illness.

If we are on the one hand searching for drugs to treat and cure mental incapacitation, and on the other looking for chemical warfare agents to produce human incapacitation, is it unreasonable to seek conscience-changing chemicals that produce benign effects at little or no physiologic cost? Can we find a substance that will make men more agreeable, trusting, friendly, and hopeful? Can the quality of intellectual performance be improved by drugs without a corresponding deficit?

I suggest that the prelude has been completed in this epoch and that the future possibilities are unlimited, or limited only by the imperfections of the imagination of man himself. The last great frontier of medical research, the chemistry of the brain and behavior has been breached, and the way is open to unsuspected goals of achievement.

Max Tishler
Merck Sharp & Dohme
Research Laboratories
Rahway, New Jersey

Impact of Research on the Growth of Medicinal Chemistry

Recently I had the opportunity to listen to a talk by Dr. Alfred Newton Richards, a pharmacologist of international repute, and now 84, on the activities in American medicine at the turn of the century. According to Dr. Richards, the years 1900–10 were exciting since "things began to happen" which were crucial in the development of the sciences related to medicine. During this decade the Rockefeller Institute was founded, as was the Rockefeller General Education Board with its enormous funds, to stimulate the growth of the medical sciences. Abraham Flexner's celebrated report (*4*) on medical education in the United States was published in 1910, and a number of journals which during the years have become influential media of publications were created. Among them were the *Proceedings of the Society for Experimental Biology and Medicine*, the *Journal of Biological Chemistry*, and the *Journal of Pharmacology and Experimental Therapeutics*. And during this same decade, American chemistry as a discipline was being aroused to contribute to medical sciences and to participate in the resolution of medical problems. Of the 4000 total ACS membership in 1909, 400 attended the annual meeting in Baltimore, and from this group 35 attended the first session of the Pharmaceutical Chemists Section, now known as the Division of Medicinal Chemistry.

No one author can accept the responsibility of showing how research has led to the present state of knowledge and achievements in medicinal chemistry. Fortunately, other papers in this symposium, contributed by men well qualified as experts in their fields, have

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filled in many details that illustrate the role played by research in the development of important classes of therapeutic agents. Accordingly, I should like to trace briefly the growth of research affecting medicinal chemistry most directly, and to discuss in a more general manner a few of the discoveries and ideas that seem to have had a major impact.

Historical Perspectives

The seventeenth, eighteenth, and nineteenth centuries were exciting periods in the history of the physical sciences. Experimental science was widely accepted and led to the uncovering of physical laws which in some instances could predict with precision the behavior of physical bodies. This period brought to the minds of educated people the beginnings of a true respect for scientific facts. Notwithstanding this state of development of the physical sciences, the same attitude in the biological and medical sciences was lacking. Philosophers and physicians during those times believed that life in a living organism is caused and sustained by a vital principle distinct from all physical and chemical forces as related to non-living phenomena. Progress in medicinal chemistry was slowed by lack of experimental inquiry and by the dogmas of vitalism.

The second half of the nineteenth century may be designated as the *genesis* of the experimental approach to the problems of medicine. Five men, Claude Bernard, Louis Pasteur, Robert Koch, Joseph Lister, and Paul Ehrlich, broke the chains that bound medicine to its past and unleashed the power of research into the fields of medical sciences. Each not only contributed handsomely to the understanding of biological processes and to the solution of medical problems, but each left a heritage to experimental medicine which still serves as a guidepost in our ever-continuing quest for control of disease. Bernard stated in his "Introduction to the Study of Experimental Medicine": "Scientific medicine, like other sciences, can be established only by experimental means, i. e., by direct and rigorous application of reasoning to the facts furnished us by observation and experiment"(*1*).

What was the armamentarium of the physician 50 years ago? A review of the Eighth Decennial Revision of the *U. S. Pharmacopeia* (1905) reveals that medicinal plants, the heritage of centuries, still dominated therapeutics at the beginning of this century. Concoctions of herbs such as ipecac, squill, ergot, capsicum, colchicum, digitalis were used as such or in galenical[1] formulations. However, it was to be expected then from the accomplishments of Sertürner and of Pelletier in their isolations of morphine and quinine respectively during the early part of the nineteenth century that chemists would seek out the compounds present in medicinal plants responsible for therapeutic activities. Surprisingly, the *Pharmacopeia VIII* contained a number of crystalline alkaloids which are still important pharmacodynamic agents. These include such alkaloids as morphine and codeine, atropine, scopolamine, quinine, pilocarpine, physostigmine, colchicine, cocaine, and homatropine.

Plants, as a source of drugs, still constitute a major activity of research. The isolation of tubocurarine by King in England (1935) and later by Wintersteiner and Dutcher of the Squibb Institute for Medical Research from tubocurare used by certain South American Indians as an arrow poison, and the isolation of reserpine from *Rauwolfia serpentina*, a medicinal drug used in India for many centuries, have resulted in important medicinal agents which amply justify the plant approach.

With the isolation of plant drugs and the elucidation of their chemical structures, another productive approach became evident. The organic chemist sought to synthesize these drugs or to synthesize molecules having some of their structural features. With the chemical structures of plant drugs as models, the chemist became the architect designing and fashioning new molecules, often improving on nature in effectiveness, tolerance, and chemical simplicity. From our knowledge of the structure of morphine we now have at our disposal a sizeable repertoire of excellent synthetic analgesics. We no longer need to fear the consequences if we as a nation were cut off from our sources of opium. Cocaine has been largely displaced by simpler synthetic substances such as procaine and lidocaine,[2] whereas the chemistry of atropine has led to a host of new and often superior drugs.

Paul Ehrlich, the Pioneer

No single individual has influenced medicinal chemistry as profoundly as Paul Ehrlich. In spite of his crucial contributions to immunology, Ehrlich recognized the limitations of immunology and proceeded to demonstrate a new approach to the control of infectious diseases through the skills of organic chemistry. Indeed, it was Ehrlich himself who proved by experimentation the inadequacy of von Behring's universally accepted view that "the tissues of man and animals are many times more susceptible to the poisonous effect of disinfectants than. . . any of the bacteria known"(*5*, *6*).

Although Ehrlich received little encouragement from his scientific contemporaries, he found a sympathetic ear within the budding pharmaceutical industry—which in Germany was to a large extent an outgrowth of the dyestuff industry. In 1890 Ehrlich wrote to the pharmaceutical manager of Hoechst:

> The purely chemical direction of medicine is at the moment neither understood nor acknowledged by the majority of my colleagues. I am, therefore, all the more delighted that you have exactly recognized the theoretical basis of my investigations and that you have approved them. I am pleased to admit this recognition gives me great satisfaction and enables me to forget the antipathy which the benzene ring, with its subtleties, is encountering particularly in clinical circles.

Ehrlich gave us a particularly stimulating idea—his side-chain theory. He imagined that cells possessed on their surface certain structures or receptors which meshed with corresponding structures on antibodies or with certain molecular configurations of synthetic chemical substances. This explained specificity of action and had led him to look for the chemicals which would act like "magic bullets" against invading organisms. We no longer accept Ehrlich's theory as applying to entire cells, but the present-day lock-and-key concepts, devel-

[1] A galenical is a remedy prepared from plants, such as an infusion or fluidextract, as contrasted with a medicine made from definite chemicals.

[2] Generic names. The trademark of Winthrop Laboratories for its brand of procaine is Novocain®, and the trademark of Astra Pharmaceutical Products for lidocaine is Xylocaine®.

oped by people such as Landsteiner and Pauling, which explain many biochemical phenomena including antigen-antibody interaction and the relationship of enzyme to substrate, recall to us the prophetic insight of Ehrlich. Most importantly for medicinal chemistry, Ehrlich established the experimental procedure which gave chemotherapy a dignified and scientific stature, equal to immunology in importance and promise for the control of infectious disease.

Ehrlich's almost successful control of trypanosomiasis by *trypan red* and *trypan blue* and his much greater success with arsphenamine[3] stimulated a segment of the German chemical and dye industry to undertake research in medicinal chemistry. It was this impetus which was largely responsible for the pre-eminence of the German pharmaceutical industry.

Notwithstanding this new emphasis on chemotherapy, progress during the 25 years following the discovery of arsphenamine was slow and, on the whole, unrewarding. The proponents of chemotherapy could only claim a few agents for the control of the protozoal diseases and for treatment of a few non-bacterial diseases. The problem of the bacterial diseases did not respond to attack by large-scale research or chemotherapy much to the bewilderment of its investigators.

Modern Research in Chemotherapy

The year 1934 was the turning point for chemotherapy. Gerhard Domagk, the pathologist, working in the laboratories of I. G. Farbenindustrie, announced the therapeutic activity of a dye, Prontosil® rubrum, in the control of experimental streptococcal infections. This discovery, followed quickly by the brilliant investigations of the French chemists, Tréfouël, Nitti, and Bovet, implicating the metabolite sulfanilamide as the active agent, gave new life to chemotherapy.

The discovery of the sulfonamide drugs had an immense influence on the more recent developments in the chemotherapy of infectious diseases, namely the discovery of the useful antibiotics. The fact that microorganisms, particularly fungi, produce substances that inhibit the growth of other microorganisms, had been known by bacteriologists before Fleming chanced to observe in 1929 the inhibitory effects of *Penicillium notatum* on staphylococci. The reinvestigation of the antibiotics for the control of infectious diseases owes its stimulation largely to the discovery of the sulfonamides.

The decade beginning with 1930 saw the introduction of modern research into a number of pharmaceutical companies in the United States. Parke, Davis already had a research institute when Merck dedicated its research laboratories in 1933. In the following year, the Lilly Research Laboratories were opened, and the year 1938 witnessed the dedication of similar institutions by Abbott and Squibb.

To the research laboratories of the pharmaceutical industry came scientists dedicated to the problems of the ill and genuinely motivated by the same ideals as those of their fellow scientists in the universities and foundations with opportunities to publish their scientific findings, to present papers at scientific meetings, and to participate in all activities accorded to scientists in academic life. These men and women have gained respect and prestige. They have become accepted by academic investigators on an equal footing.

Today, the pharmaceutical industry of the United States, with a force of over 6000 scientists, constitutes a vital factor in our quest for better therapy. During the year 1959 our pharmaceutical houses will spend more than $190,000,000 in support of their research. The ratio of research expenditure to total sales of the pharmaceutical industry is over twice as great as that of the chemical industry.

The Pharmaceutical Industry

The pharmaceutical companies recognized the need for a research organization based on active collaboration of scientists of different disciplines. In organizing its research, the pharmaceutical company had brought together under a single roof scientists diverse in training and background, all needed to carry out a program from the conceptual stage through clinical investigation. Men of different disciplines, such as chemists, pharmacologists, pathologists, and physicians, joined together for the first time to collaborate in seeking solutions to specific medical problems. The success of this new concept of collaborative research may be illustrated by some of the accomplishments in the field of nutrition. Research in this field had led to the isolation in the pharmaceutical houses of vitamin B_6 in 1938, of folic acid in 1947, and of vitamin B_{12} in 1948. Knowledge of the chemical structures of these vitamins and the synthesis of two of them demanded chemists of different skills. Nutritionists, pharmacologists, and pathologists studied the role of these vitamins in the nutrition of animals, whereas the importance of these vitamins in human health required collaboration with physicians. It is likely that several hundred scientists in the pharmaceutical industry, representing a number of different disciplines, participated in this research, collaborating with each other and banded together as a unit in search of defined objectives.

The establishment of research laboratories in American industry in the 1930's encouraged academic and clinical investigators to seek assistance of and frequently collaboration with the scientists of the pharmaceutical companies in the prosecution of their research and in transforming the results of research into useful tools for the physician. Many important contributions resulted from such collaborations. The collaboration between the late Morris S. Kharasch and Lilly research led to thimerosal and ergonovine. Lederle's and Lilly's initial liver preparations originated from a collaboration with Minot and Murphy. Putnam and Merritt established the usefulness of diphenylhydantoin in the treatment of epilepsy as a consequence of a collaboration with Parke, Davis & Company. Paul R. Burkholder of Yale furnished Parke, Davis isolates of microorganisms which eventuated in the discovery of chloramphenicol. A collaboration between E. B. Astwood, now at Tufts' Medical School, and Lederle Laboratories led to the discovery of the antithyroid activity of thiouracil and propylthiouracil. The structures and syntheses of vitamin B_1 and of pantothenic acid were the consequences of the collaboration between Merck scientists and R. R.

[3] Generic name. The trademark under which Ehrlich's experimental substance no. 606 was first sold, is Salvarsan®.

Williams and R. J. Williams, respectively. The importance of cortisone in therapy was negligible until Philip S. Hench and Edward C. Kendall of the Mayo Clinic, prompted by their own concepts, discovered the usefulness of cortisone in the treatment of rheumatoid arthritis following the first synthesis of cortisone by Sarett (7).

Research in the pharmaceutical houses has been both basic and developmental in nature. This combination of talents directed at specific objectives accounts for the rapid and efficient utilization of breakthroughs in modern therapy, whether the breakthroughs occur in industry or in the laboratories of scientists located in universities or research institutes. When a successful penetration into a new area of research is made, the modern pharmaceutical house is superbly able to muster its forces and pursue the thrust to practical advantage. Ehrlich's demonstration of methods for studying infectious diseases and their potential value in the search for new agents has been taken over and elegantly elaborated by the pharmaceutical industry. The discovery of tyrothricin in 1939 by Rene J. Dubos of the Rockefeller Institute, through his thoughtful study of the physiology of microorganisms and problems of antagonisms, the discovery of the therapeutic value of penicillin in 1940 by Chain, Florey, Gardner, and Heatley, and Waksman's researches leading to streptomycin, unleashed powerful forces in the drug companies which led to the discovery of the broad spectrum antibiotics. The discovery of the psychopharmacodynamic effect of chlorpromazine quickly brought into being an entirely new kind of pharmacology laboratory in the industry, which has already served in the development of a number of new agents with different actions for the control of mental disturbances. Polio vaccine, which owes its creation to the work of John F. Enders and of Jonas Salk, brought tissue culture techniques and a resurgence of interest in immunology to the pharmaceutical industry.

Even though the theme of this paper is directed to the impact of research, the total picture would suffer from incompleteness without a brief look at the development and production functions of the pharmaceutical industry. These latter segments have played a vital part in our history, particularly since the drugs of the past quarter century have become increasingly more complicated in chemical structure and properties. Chemists and engineers, employing at first the techniques and equipment of the chemical industry and later developing newer ones of their own, have narrowed the gap of time between the research investigator and the physician. No synthesis or isolation has proved on a commercial scale too difficult or too costly to deprive the sick of a needed drug. Without doubt, the first commercial production of cortisone by Merck from the bile acids, employing 42 consecutive reactions, was the most complicated and most costly synthesis man has carried out in factory equipment.

The situation in the pharmaceutical industry today is quite different from that of 20 years ago. Every drug company of size has a research organization capable of making new and important contributions. Each company must have a research group to grow or even to survive. Obsolescence in therapy has become a major characteristic of the age in which we live. Actually, research in the pharmaceutical company generates obsolescence, and to a degree one of its aims is planned obsolescence whereby an inadequate therapeutic agent is replaced by a better one. Most of us remember how the introduction of prednisone by Schering quickly overshadowed cortisone and hydrocortisone for the treatment of the inflammatory diseases. The broad spectrum antibiotics like chlortetracycline, discovered in the Lederle Laboratories, and oxytetracycline, first isolated by the Pfizer research staff, rapidly lost their preeminence in this country to the parent substance tetracycline. In the more distant past, the arsenicals, including the arsphenamine derivatives, once major therapeutic agents, passed into oblivion almost overnight when penicillin became available. Therapy with immune sera, once a major hope in the control of the bacterial infectious diseases, never reached maturity because of the discovery of the sulfonamides and antibiotics.

We should be proud of the praise bestowed by the public on our professions for what our predecessors of 50 years ago would have looked upon as incredible achievements in overcoming dreaded diseases. As a child, I can remember the disturbing references to rickets, scurvy, beriberi, and pellagra. Today, these diseases are so rare that the medical student in this country can no longer learn about these diseases in the teaching clinics. Once the words tuberculosis, pneumonia, and ruptured appendix were synonymous with mortal fear.

I need not remind you that the research responsible for this progress is expensive. True, the men and women of the drug industry are dedicated people who gain deep satisfaction from making a real contribution to medicine, but research must be supported from profits. Let us not forget that ours is the free enterprise system of drug research and production and it has proved its effectiveness over the past 50 years. In spite of the impressive technological advances in the Iron Curtain countries, I cannot recall a single new, modern drug discovered or developed in those countries during the past 40 years which is equal in stature to tetracycline, chlorothiazide, or tolbutamide. If research costs add significantly to the cost of a new drug, its share is an investment in the future welfare of the people of our country and of the world.

A View of the Future

From what sources did our discoveries in medicinal chemistry arise and from where may we expect them to come in the future?

A large number of our important agents have originated from investigations related to living processes. This approach has been productive and will continue to be so long as chemists have inquiring minds. Among these agents of natural origin are the vitamins, hormones, and other substances which play important roles in metabolic processes.

The vitamins as a group form an exciting chapter of the annals of the past fifty years. Today our understanding of the vitamins in nutrition and the state of technology of vitamin production are such that vitamin deficiencies on an international scale can be eliminated if the problems of world-wide logistics were solved. Since the isolation of vitamin B_{12} in 1948 no other

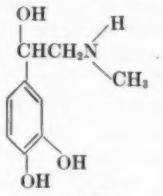
important accessory nutritional factor has been found, notwithstanding a continuity of research. In fact, it is believed by many that all the vitamins of consequence are now known. If, indeed, there are some additional nutritional factors, their physiological importance must be subtle in nature.

We still have much to learn about the hormones of the pituitary gland. These incredible hormones, polypeptides, and proteins in structures, have powerful regulatory activities which, when accessible in abundance, may well unlock the door to a new era in medicine. There are other organs still cloaked in mystery but nevertheless fascinating. We must know more about the thymus, the hypothalamus, and the spleen—the compounds they contain and why they are produced. We also need a better understanding of homeostasis and of what chemicals in the body are involved in maintaining normal blood pressure. The advances in our knowledge of nucleoproteins, their relation to viruses and to cancer should stimulate still further new approaches in medicinal chemistry.

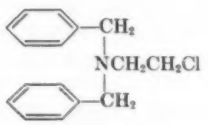
The most powerful force to ensure future progress will be new ideas. In the past, several concepts have served us well, both to satisfy in part our intellectual curiosity and to stimulate the search for greatly improved medicinal chemical agents. I have cited Ehrlich's side chain theory and the modern counterpart visualization of the structural interlocking of an enzyme with its substrate. Related to this is the extremely fruitful concept of biochemical competition. For example, in the field of enzymology, one postulates that certain congeners or isosteres resemble an essential substrate sufficiently well to fit into the receptor system of the enzyme. Where the congener is biochemically incapable of reacting like the true substrate, it may effectively block the substrate and prevent the enzyme from carrying out its function. If the enzyme is one that performs an indispensable vital function of a bacterial cell, the cell will die or at least be unable to grow. This effect was brilliantly illustrated by the work of Woods on the antagonism of sulfanilamide to *p*-aminobenzoic acid, an essential metabolite of many bacteria (*8*). From these findings stems the concept of *metabolites* and *antimetabolites*.

A most elaborate and elegant presentation of "Isosterism and Competitive Phenomena in Drugs" was given by Bovet in his Nobel prize lecture (*2*). Bovet emphasizes the importance of studies of competitive phenomena in pharmacodynamics—particularly in the pharmacology of drugs affecting the autonomic nervous system. He shows how a very large part of therapeutical chemistry depends on the relations between many alkaloids or synthetic compounds and a few substances of rather simple structure that are products of tissue metabolism and behave as hormones and chemical transmitters of nerve impulses. These substances are epinephrine and norepinephrine, acetylcholine and propionylcholine, histamine and 5-hydroxytryptamine.

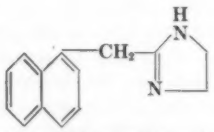
The biologically active congeners of epinephrine show either sympathomimetic activity (like epinephrine) or sympatholytic activity (antagonism). As is often the case, various drugs of this class were introduced empirically into therapeutics long before their pharmacological actions were established. These compounds fall into several chemical series—namely, phenylethylamines, phenoxyethylamines, and phenylethylenediamines. Within each of these series the structural similarities between the antagonistic molecules are evident. The degree of substitution on the amine, the suppression or displacement of the phenolic function, the closing of a ring, are factors which may reverse the pharmacological action. While the distance between the amine function and the aromatic ring may remain constant, the inhibitory molecule always has an amine group substituted by more and heavier radicals. Generally, the inhibitory molecules also have a more stable structure and a higher molecular weight.



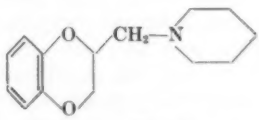
Epinephrine (Adrenalin®)
a sympathomimetic[4] drug



Dibenamine®
a sympatholytic[4] drug



Naphazoline (Privine®)
a sympathomimetic drug



Piperoxan (Benodaine®)
a sympatholytic drug

The problem of competitive agents that antagonize acetylcholine activity is more complex because of the multiple functions of acetylcholine. Acetylcholine acts as a transmitter in viscera innervated by the parasympathetic nervous system, at the neuromuscular junction of skeletal muscle and at the synapses within ganglia. A most useful fact both for exploitation in pharmacological investigations and in therapy is that compounds antagonizing acetylcholine differ according to the site of action. Thus, atropine blocks the so-called muscarinic action of acetylcholine on smooth muscle; tetraethylammonium iodide or hexamethonium block so-called nicotinic action in sympathetic and parasympathetic ganglia. The curares are specific antagonists for acetylcholine on skeletal muscle. A practical result from theoretical considerations of isosterism among curare-like compounds has been the development of succinylcholine as a short-acting, readily reversible curarizing agent.

The pharmacologists designated by Bovet as "to some extent *les enfants terribles* of physiology" were far ahead of almost everyone else in pressing the argument for the role of a chemical transmitter in the central nervous system, exactly as in the autonomic nervous system. Presumably, the psychodynamic drugs compete or interact in some way with a chemical transmitter within the central nervous system.

In concluding his review, Bovet remarks, "We see that in covering the vast field of pharmacology the

[4] "Sympathomimetic" (from the Greek): aping (the action of) the sympathetic nervous system; "sympatholytic": loosening (or destroying the action of) the sympathetic nervous system to some extent (the opposite of sympathomimetic).

structures of a small group of remarkably simple biogenic amines have led us, like the thread of Ariadne, through the labyrinth of very diversified actions and chemical structures."

Notwithstanding the beautiful and attractive concepts devised during the past fifty years, we are unable to attribute to them any of our major discoveries in medicinal chemistry. Up to now, they have been stimulating but as a whole unrewarding to the medicinal chemist at the bench. Our knowledge of the relationship of structure to biological activity has not yet reached a stage where medicinal chemists can predict with any degree of certainty the biological activity of a new chemical or can circumvent the ardous task of synthesizing large numbers of compounds. No one could have predicted that the *removal* of two hydrogen atoms from hydrocortisone would give a steroid four times as active and with marked diminution of salt retention. Nor could one have predicted, conversely, that the *addition* of two hydrogen atoms to chlorothiazide would bring about a tenfold increase in potency. Screening on a random basis is still our major approach in medicinal chemistry. Unlike the physical sciences, we have no mathematical procedures by which we can make predictions. However, we are encouraged by the progress which has been made during the past 20 years. We are beginning to sense a pattern which comes into play whenever a breakthrough in our screening program occurs. Once a breakthrough has been made, and we are faced with the problem of modifying and improving the structure, we meet it with greater confidence. We have developed over the years a perspective of the field and a capacity to be more selective in the synthetic part of our screening programs. While this empirical approach in medicinal chemistry will be with us a long while, I predict that in our lifetime we shall see some major discoveries in medicinal chemistry arising from a pure rational and predictable approach.

As an extension of this theme of empiricism, accidental discoveries must be included. We are all familiar with the term "serendipity" and some of us are reluctant to accept the great emphasis placed on it in modern research. But the facts are unmistakably clear. Our literature is sprinkled with discoveries made unexpectedly. Our latest examples are tolbutamide and iproniazid. The former was not the result of a program in search for a substitute for insulin but rather the accidental observation of a clinical study on a sulfonamide intended for the control of infectious disease. In fact, it is amazing that the lead which led to tolbutamide was not picked up at least 10 years earlier. A number of us had known for some time that a side effect of some sulfonamides was the lowering of blood sugar levels. Iproniazid was not synthesized by the Hoffmann-La-Roche chemists in their search for a psychic energizer. Rather this important effect in man which led to extensive research on the hydrazines and monoamine oxidase inhibitors, was the result of unexpected observations in the clinic with tuberculosis patients.

The essence of serendipity is the ability to recognize it. For this to occur we need investigators with trained and receptive minds. In a recent speech R. Keith Cannan remarked, "New ideas lie down the road of the unexpected and an experiment that fails may be the beginning of an understanding. But instruments and technicians are not wired to read the portent of the unexpected observation or the experiment that fails" (*3*). With the ever-growing practice of relying on technicians to carry out our experiments, Cannan's words are very appropriate. Instruments and technicians, essential as they are, must not cause a separation of the trained investigator from the immediate contact with experimentation. We must never allow ourselves to believe that mass screening by technicians can take the place of the careful experimentation by the observant, single scientist.

Role of Government Sponsorship

No account of the progress of medicinal chemistry during the past 50 years is complete without discussing the developments in Government-sponsored research and its future impact on industry and academic institutes. Beginning with the demands of World War II, research carried out in Government laboratories and research supported financially in other laboratories have increased enormously. Today, the military services, the Public Health Service, and the National Science Foundation are the major patrons of the laboratories in our colleges and universities. As much as two-thirds of the expenditures for all research performed in the academic laboratories is financed by the Federal Government.

The acceleration of Goverment-supported research has manifested itself in the rapid growth of the National Institutes of Health, the research arm of the Public Health Service. Beginning in 1930 as one institute devoted to the investigation of infectious diseases, it now consists of seven institutes charged with the responsibilities of distributing financial assistance to academic and institute investigators and of carrying out research in the areas defined by each of its institutes. The budget for the National Institutes of Health has grown from 52 million dollars in 1950 to about 400 million dollars projected for 1960, surpassing by far the expenditures for research in the pharmaceutical industry. Since a significant share of this budget is directed toward the control of disease, we now have the Government as a major participant in medical research and medicinal chemistry. With this new situation, we are faced with the problem of how to deploy most effectively the funds, facilities, and most particularly the limited number of trained people. Indeed, it may well be that the insufficiency of capable research people will impede our national programs.

Irrespective of the problems, we must recognize that these Government programs will affect each of us as private citizens and as scientists concerned with medicine. Where this enormous effort on the part of the Government will lead us is far from clear. There are those who fear that research will become not only subsubsidized by Government aid, but also dominated by Government thinking. Fortunately, there are no such signs about us or on the horizon. The important thing to keep in mind, however, is that large-scale Government support is an existing fact and it is here to stay, whatever may be the problems it creates. In my opinion, Government funds should by used to ensure financial support for a very broadly-based basic research program and to help solve our most important problem—

more trained people. If this is done, I feel confident that the stage will be set for an even more vigorous and successful attack on the complex problems in human medicine.

Let us remember that while we can synthesize compounds of all manner of structures and at times even improve on nature, we are unable to answer many simple questions arising from observations in the medical sciences. While we know how to use drugs in allaying disease, we do not know how they really function. When we begin to understand what goes on at the cellular level, our contributions to the control of diseases will be broader and more permanent.

We have come a long way during the past 50 years. We stand on the crest of a golden age in the medical sciences, viewing beyond an even greater summit. The dream of the Fountain of Youth is taking form in reality and the search for the philosopher's stone in health is no longer an idle quest. The accomplishments of the past gave us the strength and inspiration to meet the challenges of our times and the years ahead. Let us strengthen our dedication to the service of mankind so that those who inherit our responsibilities may derive inspiration from our contributions when they meet at the centennial anniversary 50 years from now.

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Arthur L. Plumley
University of Connecticut
Storrs

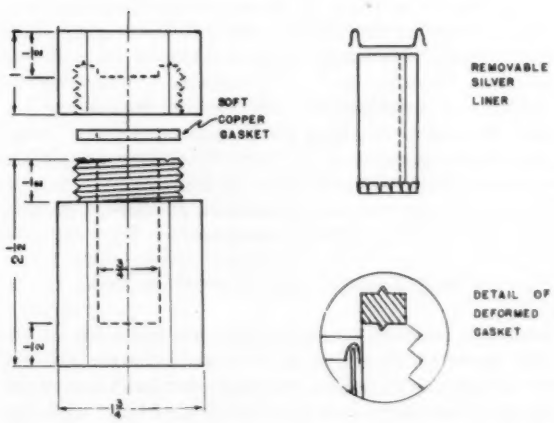
A Simplified Bomb for Hydrothermal Synthesis

Hydrothermal procedures [1,2,3] have been used with considerable success to prepare a number of alumino silicates, mixed oxides, and other compounds. Details of construction are presented for a simple bomb which costs less than $10 and may be safely operated in the laboratory.

The bomb is fashioned from 216 stainless steel hexagonal stock and has a volume of approximately 10 ml. The threaded lid is tightened by means of a wrench while the bomb proper is held in a vise. A soft copper gasket deforms into grooves machined around both the lid and the lip, thus providing a gas-tight seal. The gasket, which can be used only once, is annealed prior to use by bringing it to red heat and quenching in water. The gaskets used in this laboratory were individually machined but can be obtained commercially.

For convenience in removal of the products and to prevent contamination of the sample, a liner may be used with the bomb. Shown is a removable silver liner made from 0.020 silver sheet, the seams of which are secured with silver solder. Platinum, copper, and glass liners have been used, but silver is most suitable for the alkali slurry used in the alumino-silicate preparations in this laboratory.

The bomb was used successfully in a dozen or more runs at temperatures up to 400°C with a one ml paste mixture of the required oxides. While the design of the bomb is such that it could withstand even greater pressures, it is suggested that some form of shielding be used during the operation, such as surrounding the bomb and heater with concrete blocks and sand bags.



The construction of similar hydrothermal bombs has been described in the literature.[1,4]

This work was performed on a project supported by the U. S. Atomic Energy Commission.

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R. J. Gillespie
McMaster University
Hamilton, Ontario, Canada
and **C. Solomons**
Imperial College
London, England

Molon—A New Concentration Unit

The concentrations of solutions can be expressed in a variety of different ways. Physical chemists generally use one of the following concentration scales:

(1) Molality, m, moles of solute per *kilogram of solvent.*
(2) Molarity, c, moles of solute per *liter of solution.*
(3) Mole fraction, x, moles of solute divided by total number of moles in the system.

We have found in our work on solutions in sulfuric acid[1] and other non-aqueous solvents that it is often convenient to express concentrations in another way, namely, as moles of solute per *kilogram of solution*, i.e., in mole $kg_{solution}^{-1}$ units.[2] This unit has not been widely used and has no special name or symbol. We suggest the symbol w, derived from weight concentration, and the name *molon*, derived from mole/kg solution.

There are several advantages in expressing concentrations on this new scale.

Concentrations in *molon* units are independent of the internal state of the system. Mole fractions and molalities suffer from the disadvantage that they can have more than one value in cases, for example, where the solute reacts with, or is solvated by, the solvent or where the solvent is self-dissociated. Thus one can calculate a stoichiometric molality on the assumption that the solute dissolves unchanged or various "true" molalities depending on the particular assumption made concerning the internal state of the system. In sulfuric acid many substances behave as bases, e.g., acetone ionizes in the following manner:[3]

$$(CH_3)_2CO + H_2SO_4 = (CH_3)_2COH^+ + HSO_4^-$$

And it is possible to express the concentration of the solution either in terms of the stoichiometric molality of the acetone (in effect, one assumes that the acetone dissolves unchanged) or in terms of the "true" molality of the hydrogen sulfate $(CH_3)_2$ COH·HSO_4. Moreover since sulfuric acid is appreciably self-dissociated,[1] the molality of a solute depends on whether or not the self-dissociation species are regarded as constituting part of the solvent.

Concentrations in *molon* units are independent of temperature. Volume concentrations such as molarity are independent of the internal state of the system but are temperature dependent and thus have the disadvantage that a given molecular concentration has a different volume concentration at different temperatures.

When solutions are made up by weight their concentrations can only be expressed in molar or other volume units if the densities of the solutions are known. Sometimes, as has been the case for some sulfuric acid solutions, the densities are not known or are not known with very great accuracy. Some workers have attempted to avoid this difficulty caused by the lack of knowledge of the density of a solution by using the density of the pure solvent to calculate an approximate or "pseudo" molarity. As they have often not been careful to distinguish this quantity from the true molarity, confusion has sometimes arisen. This method of expressing concentrations should therefore be avoided. If concentrations are expressed in *molon* units they are readily converted to molarities if, and when, the densities of the solutions are available, by means of the simple relation:

$$c = \rho w$$

Thus concentrations expressed in molon units have the advantage that they are independent of the internal state of the system and depend only on the weights of the materials used to make up the solution; they are independent of temperature; and they are readily converted to molarities by the above simple relation.

[1] Gillespie, R. J., and Robinson, E. A., "The Sulphuric Acid Solvent System," Chap. 9, in "Advances in Inorganic Chemistry and Radiochemistry," Vol. 1, Academic Press, Inc., New York, 1959. Gillespie, R. J., *Reviews of Pure and Applied Chemistry*, **9**, 1 (1959).

[2] Gillespie, R. J., Oubridge, J. V., and Solomons, C., *J. Chem. Soc.*, 1804 (1957).

[3] Gillespie, R. J., and Leisten, J. A., *Quart. Rev.*, **8**, 40 (1954).

Editor's Note:

We call readers' attention to an alternate nomenclature, "Molel," proposed for the same unit by J. M. Thoburn in his article, "Weight Titrations Revived," this Journal, **36**, 616 (1959) (December). Readers who have encountered other terms designating the same unit are invited to communicate with the Editor.

Carleton S. Spear
Continental Classroom
National Broadcasting Company

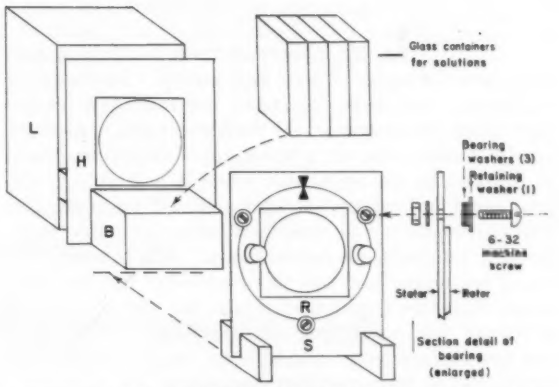
A Demonstration Polarimeter

In the course of televised lectures for Continental Classroom-Modern Chemistry it was found desirable to demonstrate both the phenomenon of optical activity of organic compounds and the instrument by which it is measured.

The polarimeter described here was constructed within three hours from materials such as heavy art cardboard, brass bolts and washers, and two squares of Polaroid sheet. The tools used were a sharp cutting knife, file, saw, and screw driver. The instrument is versatile. Several solutions in separate containers may be placed together and compared one at a time. The purpose and function of the instrument can be explained while describing and assembling the completed component parts on the lecture table. The apparatus is shown in the figure. The stator and rotor of the dial assembly (analyzer) are made of two pieces of art cardboard. Concentric holes, 5 in. in diameter, are cut with a sharp knife in each. The stator may be one foot square, and the rotor a ten-in. diameter circle. The outer edge of the rotor is smoothed by using a flat file in order to provide smooth, even contact with the three bearings. The surface and edges of the rotor are sprayed with clear lacquer before the Polaroid square is fastened to it. Corks, fastened with adhesive, are added for convenience of operation. Construction of the bearings is indicated in the Section Detail. Index marks for stator and rotor are small triangles cut from black adhesive masking tape. The markers can easily be repositioned for calibration. The finished assembly becomes the analyzer. It stands erect in the slots in two wooden supports. Small wedges hold the supports in place.

Where shop facilities are available, more durable materials than smooth cardboard can be utilized. Bigger squares of Polaroid sheet can be used if necessary. The apparatus is relatively simple and inexpensive and can be constructed by students for use in laboratory experiments.

The rectangular glass containers used in the polarimeter are of extremely fine quality, but are correspondingly expensive. They measure 2 × 5 × 10 cm (inside dimensions) and were obtained from Klett Manufacturing Company, 179 East 87th Street, New York 28, N. Y. Square containers such as battery jars or square bottles can be used. Good results are obtained when using beakers and ordinary round bottles by making observations at the vertical axis of the containers. The rotor (analyzer) may be graduated in degrees if quantitative measurements of rotation are desired.



L represents a light box (photographic printer) with opal glass. H designates a foot-square cardboard holder for a 6 × 6 in. square of Polaroid sheet. (The latter is fastened by Scotch tape tabs in front of the 5-in. diameter hole.) This assembly becomes the polarizer. B is a block support for the solution containers. S and R represent stator and rotor of the dial assembly made of cardboard.

Since the light source was not monochromatic, trials were made with optically active solutions to determine a common effect of rotation. A sharp transition in color, blue to red, was selected as the "end point" when the analyzer is turned. This effect can be observed by a class.

The polarizer and analyzer are first crossed to shut out light transmission. Corresponding black tabs are positioned on the rotor and stator to mark this point. A container of water is placed on the block with no change in light transmission. A two-molar solution of levulose is placed on the block to the left of the water, and a similar solution of dextrose is located on the right of the water container. Light is transmitted through both solutions.

The dial is rotated counterclockwise until the sharp blue-red transition appears for levulose. When the dial is rotated clockwise, the sharp transition from blue to red occurs in the light transmitted by the dextrose in the right hand container. .

The liquids may be removed and unknowns substituted. Cane sugar solutions, syrups, honey, as well as a number of other organic compounds may be used. The magnitude of the angles of rotation observed from the solutions used for demonstration varies between twenty and seventy degrees. If suitable containers, whose inside measurement can be determined, are available, perhaps good relative values for optically active solutions can be obtained.

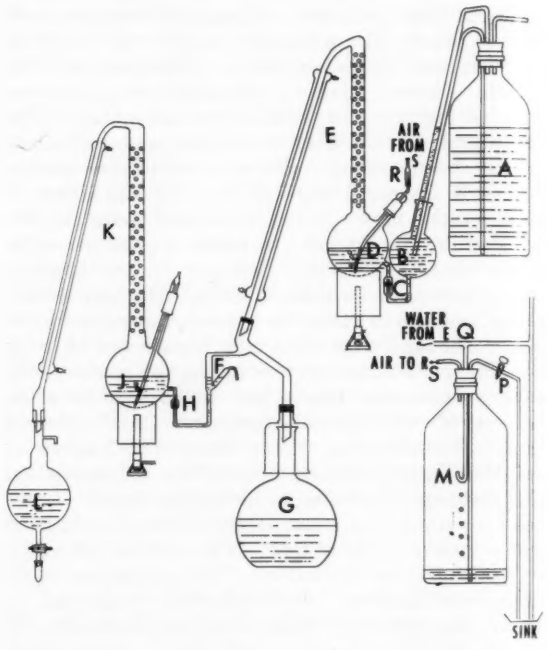
Jay E. Taylor
University of Nebraska
Lincoln 8

An Apparatus for the Continous Production of Triple Distilled Water

In this laboratory there has been a constant need for water of very high purity. In designing equipment to answer this need the following factors were taken into account: (1) the highest purity product should be obtained; (2) a minimum of attention should be devoted to the apparatus while it is running; (3) time spent on upkeep or repairs should be negligible. The combination still described below has very satisfactorily fulfilled these requirements. There is an additional less important but quite amusing feature associated with this apparatus; this is the high "comment quotient" which, because of bubbling permanganate and the various tubes and siphons, often exceeds that stimulated by more complex apparatus.

The cycle starts with the five gallon reservoir *A* in which tap distilled water is stored. The maximum length of running time of the still is determined by the capacity of this reservoir. The water from *A* siphons continuously into container *B* and the level is kept constant with the leveling device as shown. From *B* the water passes through tube *C* and into the one liter distillation pot *D* which contains dilute basic permanganate. The glass check valve at *C* prevents backsurge of the water from *D* into *B*. Using a Bunsen burner the water in *D* is distilled through the Vigreux column and condenser at *E* and into *F*. The Bunsen burner flame is protected from currents of air as shown and the rim around flask *D* prevents overheating of the glass area above the boiling water. The purpose of the tube at *F* is to provide a constant supply of water for the distillation pot at *J*. Since it is quite difficult to set the rate of distillation of water from *D* exactly equal to the rate of distillation from *J*, an overflow reservoir is provided at *G* so that still *D* may be run faster than *J*. The air space seen in *F* prevents possible contamination of the overflow distillate because of back diffusion of water from pot *J*. The check valve at *H* prevents backsurge of the boiling water. Pot *J*, containing very dilute sulfuric acid is heated similarly to *D*. The final distillate passes through the Vigreux column and condenser at *K* and is collected in the reservoir *L* which is equipped with a greaseless stopcock.

One serious problem associated with any distillation is bumping. This is prevented by an inverted 2 mm capillary tube in *J*. It is necessary to shake this capillary so that it will at least be partially filled with air each time before the still is started. Due to the greater tendency of basic solutions to bump, a more elaborate setup is used in *D*. The cooling water passes first through the condensers *E* and *K* and then into the air reservoir *M*. Pressure equal to a head of water of the height *QM* develops and the overflow water passes out through the T-tube at *Q*. The air trapped very slowly escapes through the fine capillary at *R* and bubbles into the bottom of pot *D* thereby providing a continuous flow of bubbles to prevent bumping. The capillary at *R* should be sufficiently small so that at least twenty hours are required to displace the air in *M*.



The organic matter which inevitably accompanies distilled water produced from central steam supplies is oxidized by the basic permanganate solution in *D*. This solution is made by adding 3–5 ml of saturated $KMnO_4$ and the same amount of 1 *M* sodium or potassium hydroxide each time the pot is cleaned out. For best results, the pot *D* should be cleaned after each emptying of water reservoir *A* simply by siphoning.

The contents of pot *J* include 2–3 ml of concentrated sulfuric acid added to neutralize any amines or other basic substances which may possibly distill from *D*. This solution need not be changed for long periods.

The water produced is of high quality. The conductivity of the water will depend on the care which has been taken in preventing contact of the water with carbon dioxide of the atmosphere. If superconductivity water is desired, it would be well to replace the Bunsen burners by electrical resistance heaters and to protect all openings to the atmosphere by tubes containing Ascarite, soda lime, or other carbon dioxide absorbent.

Organic and mineral impurities only have been of prime concern in this laboratory so this precaution has not been observed.

This apparatus accomplishes its purpose in a highly efficient and trouble-free manner. To turn it on in the morning the stopcock at P is closed, the condenser water is turned on, and the burners are ignited. The only care required during the day is to empty the reservoir L of triple distilled water when it becomes filled. At the close of the day the burners are turned off, stopcock P is closed, and the condenser water is turned off. The antibumping capillary should be lifted up above the surface of the water in flask J for a short time after the distillation stops, and then it will require no attention the next morning.

To refill the five gallon reservoir at A the distillation is allowed to continue until the siphon in tube AB breaks. Tap distilled water is then run into A until the bottle is filled and the water is forced back into siphon AB. The stills D and J need not be stopped for this operation.

It may be noted from the diagram that the burners are directed against bare glass. The advantage is maximum heat exchange. If this setup is used, it is important that the flasks do not go dry after depletion of the reservoir A, or the stills may crack.

* * *

GUEST AUTHORS
Ralph Daniels, Clyde C. Rush, and **Ludwig Bauer**
University of Illinois
Chicago 12

Textbook Errors, 24

The Fehling and Benedict Tests

The use of the Fehling and Benedict tests for detecting aliphatic aldehydes is recommended by all writers of textbooks[1] and laboratory manuals in organic chemistry. These tests employ a solution of copper(II) ion in alkaline medium. To keep the test solution homogeneous, the concentration of copper(II) ion is held low, through complex formation with tartrate ion in the Fehling test solution and with citrate ion in the Benedict test. The tests proper involve the addition of a substance to the test solution and heating the reaction mixture to 100°C.

According to the standard textbooks, aldehydes are oxidized to the corresponding carboxylic acids with reduction of the copper(II) ion to copper(I) oxide, which appears as a yellow to red precipitate. When subjected to the same treatment, ketones are not supposed to reduce copper(II) ion and the test solutions retain their blue color. Therefore, these test reactions, if the texts are interpreted literally, are presumed to differentiate between aldehydes and ketones.

This simple interpretation for the test reactions is not in accord with experimental facts. While the test reactions are positive for aldoses and reducing sugars, we have found that extrapolation to simple aliphatic aldehydes is unwarranted. Exploratory experiments in our laboratory have shown that under standard conditions[2] the changes observed in treating a substance with the test reagents fall into three categories:

(1) A colorless aqueous solution admixed with a yellow to red precipitate results. The precipitate is Cu_2O; its formation represents a positive test.

(2) Complex changes occur, with formation of a red or dark-brown, gummy precipitate. In this case, the supernatant liquid may be blue, green, brown, yellow, or orange.[3] Nevertheless, this constitutes a negative test because experiments in our laboratory indicate that the precipitate is *not* copper(I) oxide. Apparently these changes have been mistaken for a positive test.

(3) The blue solution of the test reagent remains, with or without the presence of a colorless immiscible organic layer. This is a negative test.

We subjected several aldehydes and ketones to these tests and found that carbonyl compounds could be classified according to the color changes described above

Category (1): glucose and the reducing sugars, α-hydroxyadipaldehyde, glyoxal, and pyruvic aldehyde.

Category (2): acetaldehyde, crotonaldehyde, cinnamaldehyde, and aldol.

Category (3): benzaldehyde and aromatic aldehydes in general, isobutyraldehyde, 2-ethyl-hexanol, and acetone.

A tentative conclusion can be drawn from these preliminary experiments: Copper(II) ion in Fehling or Benedict test solution will be reduced to copper(I) oxide by α-hydroxyaldehydes, α-hydroxy ketones and α-ketoaldehydes. Other aldehydes and ketones do not produce copper(I) oxide. We have found that the Tollens' test reagent (an aqueous solution of diammine silver(I) hydroxide) is infallible for distinguishing aldehydes from ketones.

Suggestions of material suitable for this column and guest columns suitable for publication directly are eagerly solicited. They should be sent with as many details as possible, and particularly with references to modern textbooks, to Karol J. Mysels, Department of Chemistry, University of Southern California, Los Angeles 7, California.

[1] Since the purpose of this column is to prevent the spread and continuation of errors and not the evaluation of individual texts, the source of errors discussed will not be cited. The error must occur in at least two independent standard books to be presented.

[2] The standard conditions employed in our laboratory involve heating the reaction mixture for three minutes *in* a boiling water bath. Further experimental details will be reported fully when this study is completed.

[3] It is noteworthy that the Fehling test solution gives rise to more extensive changes than does the Benedict test solution. In the case of the Fehling test, a trace of copper (I) oxide may be formed if an excess of test compound is employed.

Paul W. Morgan
Textile Fibers Department
E. I. du Pont de Nemours & Co., Inc.
Wilmington, Delaware

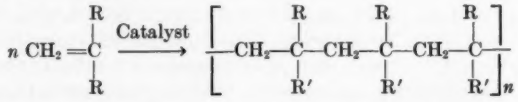
Models for Linear Polymers

One of the steps in teaching the general character of polymers and polymer formation is portraying the concept of long chain molecules. Polymer chains may be represented by linked paper clips or plastic "Pop-It" beads in various colors. Blackwell[1] has described the latter system in detail. These models are simple and most helpful, but somewhat static and lifeless.

A group of more active models, which has been used successfully before grade and high school students, is based on the use of small bar magnets as the connecting links for a lighter material representing the body of the polymer intermediate. (The use of magnets as connecting links in models for coordination compounds has been described.[2])

Models for Addition or Vinyl Polymers

Many well-known synthetic polymers are made by the catalyzed addition of unsaturated monomeric substances to themselves to form chains without any by-product. Some of these are polyethylene, polystyrene, poly(methyl methacrylate), polyacrylonitrile, and poly(vinyl chloride).



R and R′ may be hydrogen or some other substituent group.

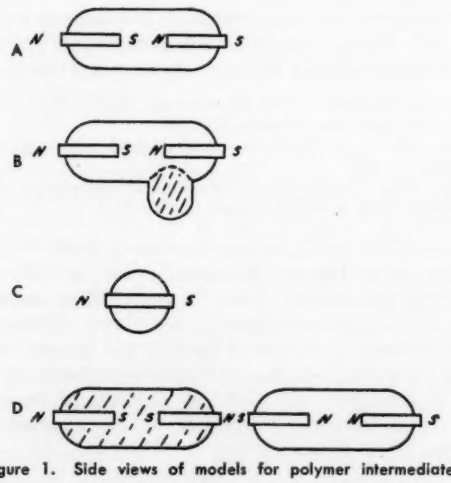


Figure 1. Side views of models for polymer intermediates.

Models for this group of polymers can be made by inserting small bar magnets in sections of a light body material so that a north and a south pole is exposed in each "molecule" of intermediate (monomer). Alternatively, one end may contain a magnet with constant polarity and the other a nail head. (Figs. 1A and 1B.)

Appropriate coloring or structural appendages can be added to indicate the R groups and their position. A single bar magnet can be used to represent an intermediate molecule, if the center is covered with a ball or cylinder of inert material (Fig. 1C).

For a demonstration a dozen or so monomer models are placed in a shallow paper bag and interacted by moderate shaking or tumbling. The operator then pulls from the bag slowly a chain of linked units (Fig. 2). The actual end-to-end contact requires a little manipulation in the bag as the chain grows, but this does not detract from the effect. The single magnet type (1C) will form chains when they are rolled together on a table surface.

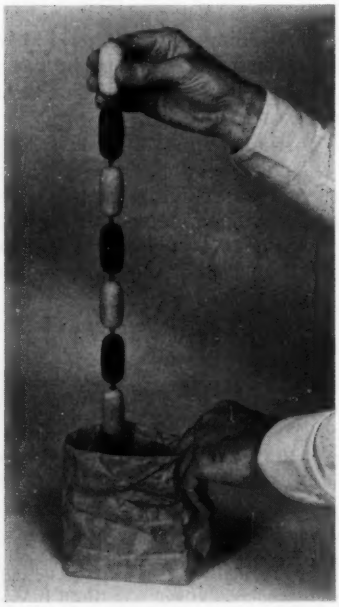


Figure 2.

Models for Condensation Polymers

Many condensation polymers are formed by the interaction of two complementary intermediates to form a chain in which the two components alternate, as in many nylons, polyesters, and polyurethanes. These

[1] Blackwell, R. Q., J. Chem. Educ., **34**, 500 (1957).
[2] Wendlandt, W. W., J. Chem. Educ., **34**, 223 (1957).

are often spoken of as AA-BB structures. Condensation polymers are also formed from intermediates which contain the two interacting groups at opposite ends of a single intermediate molecule. Such polymers are proteins, cellulose, and the nylon, polycaprolactam. These are designated AB-AB condensation polymers. (AA could be hexamethylenediamine; BB, adipic acid, and AB, ϵ-aminocaproic acid.)

The models for addition polymers can serve as well for AB-AB condensation polymers. A model for the AA-BB type is prepared by making two groups of monomers, one with both outer poles being north and the other with the outer poles being south. (Fig. 1D.) To save magnets one group could have iron screws or nails as the inserts. The difference between the two intermediates should be indicated by color, shape, or material of construction. The demonstration is carried out as before, using an equal number of each type of monomer. A chain having an alternating sequence should form (Fig. 2). This is a good companion experiment for the demonstration of condensation polymerization.[3]

The analogy between these models and polymers or polymer behavior is schematic as well as inaccurate in many ways. For instance, they do not show the elimination of a small by-product molecule which accompanies a condensation reaction. The purpose is not exactness, however, but the dramatization of the general concept of linear polymers. The scheme can be elaborated to show copolymerization, branching, and chain termination in condensation polymerization by monofunctional materials, or failure to reach high polymer because of nonequivalence of complementary reactants.

Excellent magnets ($^1/_8'' \times {}^3/_{16}'' \times {}^4/_8''$) of Alnico V, alloy may be obtained inexpensively from Sunset House 100 Sunset Building, Beverly Hills, California. Balsa wood is readily purchased in small pieces from hobby and model shops. Other possible body materials are sponge rubber, foamed polystyrene, urethane foams, and papier-mâché.

[3] Morgan, P. W., and Kwolek, S. L., J. Chem. Educ., **36**, 182, 530 (1959).

Ralph L. Dannley
Western Reserve University
Cleveland, Ohio

A Talk and Demonstration Kit for Adult Non-Technical Audiences

In a previous article[1] a talk and a demonstration kit for high school students have been described. The interest shown in this endeavor encouraged the author to prepare a second kit. This second kit is specifically planned for presentation to adult audiences although nothing in its nature precludes its use for younger people. It also differs from the first in that the kit serves as a lectern for the talk as well as a packing case.

This lecture, titled "A Better World Through Chemical Research," discusses and demonstrates some of the newer chemical products now available and qualitatively predicts improvements which may be expected in the future. The demonstrations include preparation of a polyurethane foamed resin, comparison of the physical properties of silicon polymers with corresponding hydrocarbons at low temperatures, exhibition of the adhesive strength of epoxy resins, comparison of detergents and soap in hard water, softening of water with chelating agents and ion exchange resins, and the conversion of solar energy to electricity.

Mimeographed directions have been prepared which are so detailed that any qualified chemist can present the talk and demonstrations with less than an hour's preparation. Since the directions are similar in general organization to those described for the first kit,[1] only major changes will be described in any detail. The mimeographed directions consist of the following sections:

Instructions to the speaker

Outline of the talk

Directions for unpacking and setting-up—This section has been introduced because the kit case is sufficiently complex so that in its first use a speaker might overlook the purpose of some of the components.

Directions for the demonstrations

Chemistry of the demonstrations

Complete talk

Directions for packing equipment

Directions to stockroom men

Equipment and chemical supplies—Many requests are received by the speaker for sources of the equipment and supplies. This section has been added primarily to aid the speaker in answering these questions properly. It also simplifies reordering the supplies by the stockroom men.

The case is constructed of masonite and one-half in. plywood. The interior is partitioned to hold a Dewar, bottles, beakers, and 15 ml graduates firmly to prevent breakage. Three removable packing units slide into slots in the case.

Presented before the Division of Chemical Education at the 136th Meeting of the American Chemical Society, Atlantic City, September, 1959.

[1] Dannley, R., J. Chem. Educ. **35**, 457 (1958).

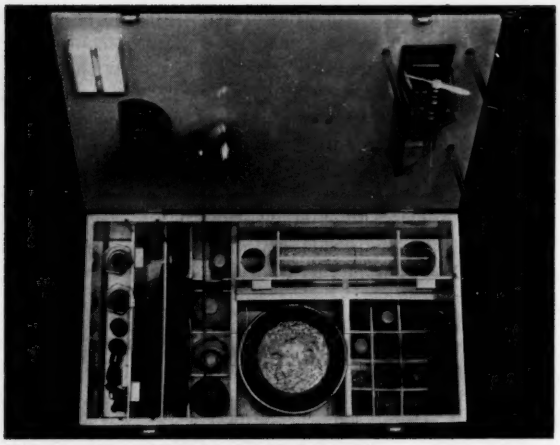


Figure 1. Kit assembled for traveling (top view).

One of these sliding units acts as a packing section for four large test tubes inserted horizontally through appropriate holes. This section when hung on the exterior of the audience side of the case serves as a test tube rack. The test tubes can be removed from their horizontal position and inserted in normal vertical position through a second series of holes.

After removal from the case, the second sliding section is hung on the exterior of the speaker's side of the case. This unit holds a hammer, chisel, forceps, spatulas, tubes of silicone and petroleum oil, and two 50-ml graduates. Thus it serves as a convenient rack for the equipment during the talk as well as a packing unit.

The third sliding panel is merely a board on which a 50 ft. extension cord is wrapped. Since electrical outlets are seldom convient to the speaker's table, this cord is necessary to provide current to the lamp for the solar energy unit.

The lid of the case is restrained by a dog leash which is readily unsnapped. The hinges are a common screen slip-type which are readily disengaged to permit turning the lid upside down. When inverted, appropriate cleats prevent the lid from sliding off the case. Reversing the lid presents a formica-covered surface on which is mounted the solar energy unit with its flood light, and a wooden anvil needed in the epoxy resin demonstration. The case, therefore, becomes a convenient lectern with a practical working surface. The kit is shown packed (Fig. 1), and set up (Fig. 2).

Polyethylene bottles have been used as containers for the liquids because of their lightness of weight and unbreakability. The only glass bottle is used for the carbon tetrachloride solution of sebacyl chloride needed for the interfacial polymerization.[2]

Each bottle is clearly labeled with a code letter for its position in the sequence of experiments, the chemical name of its contents, and the quantity to be used in the experiment. This complete labeling makes it possible for the speaker to perform the experiments without referring to any directions.

Culture tubes were used as containers for the silicone and petroleum oil because their screw-caps eliminate spillage. A metal Dewar is used to prevent breakage. Small pharmaceutical graduates are used because the wide mouth simplifies filling. Paper towels and a bottle of benzene are supplied to permit the speaker to clean up any spillage which is not water soluble.

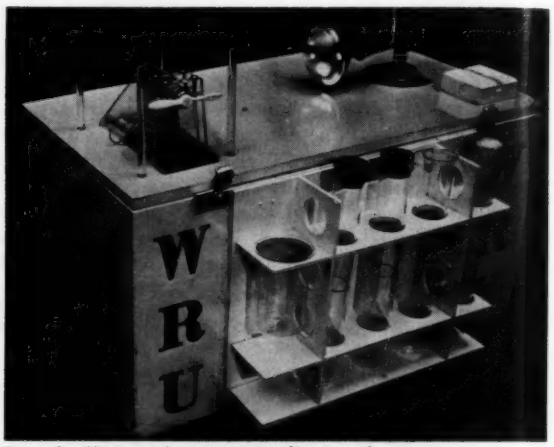


Figure 2. Kit set up for presentation (front view).

Acknowledgment

Appreciation is hereby expressed to the Cleveland Foundation for funds supporting this activity and to Dr. John Yeager and the National Carbon Laboratories of Cleveland for the photographic work.

[2] Morgan, P. W., and Kwolek, S. L., J. Chem. Educ. 36, 182 (1959).

Paperbound Books in the History and Philosophy of Science

A new bibliography of paperbound books in the history and philosophy of science has been prepared as a guide for high school science teachers. This 16-page, mimeographed bibliography lists approximately 200 titles and includes an estimate of the difficulty of the content and language of each book. High school science teachers may obtain a copy of the biblography by sending a request to the compiler, Leo E. Klopfer, 71 Batchelder House, Harvard Graduate School of Education, 7 Kirkland Street, Cambridge 38, Mass. Please enclose 10¢ to cover mailing expenses.

Arthur H. Livermore
Reed College
Portland, Oregon
and **Laurence E. Strong**
Earlham College
Richmond, Indiana

A Writing Conference for CBA High School Chemistry Project

Seventeen chemistry teachers spent six weeks at Reed College during the summer of 1959 writing a new kind of introductory chemistry course. About 1000 pages of rough drafts were written. This is now being edited. A first text volume (five chapters and an appendix) and a volume of laboratory experiments have been printed. As a result, nine high schools are engaged in a year of testing a different approach to the introduction of students to chemistry. Although only part of the material needed for a year course is so far assembled, it is planned that text and laboratory instructions will be completed as needed during the year. The trial course is being used to provide a basis for further revision of course organization and materials.

Course Proposal

Clearly any attempt to design a new approach to the introduction of students to chemistry must make certain assumptions about the nature of chemistry and of students. Modern chemistry consists of facts connected by ideas. These ideas are both powerful and intriguing. High school students can deal logically with these ideas and will derive genuine satisfaction from doing so. So far as can be anticipated, such an approach will be particularly attractive to the more thoughtful students, but it should be meaningful even to the average ones.[1]

The point of view is that chemical reactions are discussed in terms of the initial and final states of the reacting substances. A student thus is introduced to the properties which characterize the initial reactants and the final products. This is the basis for emphasizing the fact that the relation between these initial and final states is not an obvious one, and that, hence, a major intellectual problem in the study of chemistry is dealing with this aspect of each chemical reaction. Properties are then presented in relation to various structures, and the phenomena attending chemical change discussed in terms of contemporary ideas about structural changes.

The framework proposed for dealing with the intellectual problem is the idea of chemical bonds. Chemists deal with aggregates of atoms and the properties of these aggregates are largely determined by the forces that operate between the atoms and that are, in a sense, responsible for the aggregation. For the purposes of the course, bonds are divided into three main types: covalent, metallic, and ionic. It is pointed out that the divisions among the three are not free from overlap, for example, polar covalent bonds.

To support the chemical bond theme a number of topics are introduced. Among these are atomic orbitals and the geometry of orbitals. Hybridization of orbitals is discussed, and the various possibilities for s and p hybrids presented. A distinct innovation to introductory chemistry is a discussion of metallic bonds. This topic is dealt with through the electron gas model. A brief discussion is also devoted to the packing of atoms into crystals.

It would almost certainly be unrewarding for an introductory course in chemistry to devote its major attention to chemical theory. While the proposed course is developed around a major conceptual scheme, this is used as a way of illuminating a variety of chemical phenomena. Descriptive chemistry in the course includes such topics as carbon chemistry and a discussion of some simple substitution reactions, hydrides, salts, acids and bases, metals and alloys, interhalogen compounds, and other items. For the writing of chemical formulas, the Stock nomenclature is used, and in straightforward ionic substances ion charge is indicated, e. g., $Mg^{++}(Cl^{-})_2$.

A course which differs as radically from the usual format as this one needs its own laboratory experiments. Accordingly, work is underway to design effective experiments, but with detailed directions kept to the minimum. Students will be encouraged as much as possible to devise their own procedures. Professor H. O. Neidig has assumed major responsibility for this part of the course.

The important hope is that the experiments will encourage students to think about their observations. A major premise of the course is that conceptual schemes such as atoms, bonds, energy, etc. are useful because they provide logical connections among otherwise diverse chemical phenomena. The laboratory and lecture experiments should involve the students in this enterprise.

Experiments have been designed to deal with questions of observation, compound composition, solubility classification, separation of a mixture, and compound stability. As a part of the writing conference, a group of high school students was used to test a number of

Presented before the Division of Chemical Education at the 136th Meeting of the American Chemical Society, Atlantic City, New Jersey, September, 1959.

[1] See the report of the preliminary form of the course, "Chemical Bonds," evolved at the Reed Conference of 1957, STRONG, L. E., AND WILSON, M. K., THIS JOURNAL, **35**, 56 (1958).

The Wesleyan Conference in 1958 (see THIS JOURNAL, **36**, 90 (1958)) examined the proposal in more detail. Several high school teachers taught experimental courses following this approach. Their experiences were shared with others by means of a "Newsletter" published through the efforts of Harry F. Lewis.

The initial trials by teachers proved that the major need in this experiment was study materials for students. To fill this need, a NSF grant was made to support the conference here described.

the new experiments. These students were given laboratory instruction by some of the high school teachers participating in the conference. Work is continuing on other experiments and demonstrations.

Unresolved Issues

When a group contemplates the problems of an elementary presentation of chemistry in the light of contemporary thinking a number of questions are evident. Thus, it seems quite important to make use of energy relations in presenting atomic and molecular structure. But what is energy? Can students be given an elementary definition that is at the same time meaningful and reasonably precise? It is desirable to have the use of energy jibe with its use in physics as well, but simply to define energy as capacity to do work seems somewhat inadequate. Presumably it is undesirable to give the impression that energy is one of the components of a reaction on the same footing as the reagents.

Another issue related to energy is that of chemical equilibrium. At this level of instruction Le Chatelier's principle can be helpful. Should equilibrium constants be used? It is possible to discuss equilibrium exclusively on a free energy basis rather than by equilibrium constants. This choice would tie rather simply into the other energy discussions. It is even possible to link free energy to the concept of potential energy. One suggestion is to develop the idea of "Bond Improvement Energy" as a way of talking about the relative stability of substances.

Should electrons be presented as particles or as charge clouds? Probably, at present, students grow into the notion that electrons are particles. Later on it is pointed out that electrons sometimes exhibit wave-like properties. Most students seem to continue with the view that electrons are particles which occasionally wave. Perhaps this course can attempt to plant the concept of electrons as constructs with both wave and particle properties.

Oxidation-reduction is a topic quite commonly given substantial treatment in most present-day courses. Does the classification of certain chemical reactions as oxidation-reduction rest either upon clearly defined experimental procedures, or upon well-established theoretical principles? Several chemists have pointed out difficulties with the usual attempts at classification.[2] It was tentatively agreed by the members of the writing conference to treat oxidation-reduction as an arbitrary classification scheme without any particular chemical significance. The topic is discussed largely as an aid to the balancing of certain types of chemical equations.

Present Status of the Project

For a committee to write a textbook is a rather distinct departure from usual practice. Considerable skepticism has been expressed at the proposal for seventeen people to organize and write a new chemistry course. It is too early to say that the committee approach to such an effort has succeeded. At least some material has been produced. Those who participated did come to the conclusion that the group effort was feasible. Other groups should feel encouraged to try this method.

Conference personnel included nine high school and eight college teachers.[3] In addition, a number of others visited for a few days during the session. These visitors presented seminars, criticized the writing, and worked on special facets of the course. The participants were assigned to one of five different writing groups. Each group was asked to write material including diagrams, questions, problems, and bibliography for a particular part of the course. One of the five groups was given the problem of working out suitable laboratory and lecture experiments.

Each of the nine schools represented at the conference agreed to carry out a supervised trial of the course in one or more classes during the 1959–60 academic year. The schools selected are:

Central High School, Phoenix, Arizona
Chester High School, Chester, Pennsylvania
Grant High School, Portland, Oregon
Lawrenceville School, Lawrenceville, New Jersey
Leonia High School, Leonia, New Jersey
Los Angeles High School, Los Angeles, California
Shortridge High School, Indianapolis, Indiana
Sunset High School, Beaverton, Oregon
University of Illinois High School, Urbana, Illinois

In these schools about 800 students are involved. Some classes are selected as to ability while others are not. Each teacher is supplied with texts for individual students and with teacher's guide material. A set of polystyrene foam models have been prepared for each school, and a small number of reference books have been arranged for each teacher. The atomic and molecular models are based on the recommendations of Sanderson,[4] but teachers are encouraged to use a variety of models.

Three other educational institutions are trying the course on an informal basis. These schools are: Buckingham School, Ohio Wesleyan University, and Kenyon

[2] Vander Werf, C. A., Davidson, A. W., and Sisler, H. H., J. Chem. Educ., 22, 450 (1945).

[3] Full-time participants in the 1959 Reed Conference on High School Chemistry were:

Arnold E. Bereit, Central High School, Phoenix, Arizona
Kenneth E. Borst, Leonia High School, Leonia, New Jersey
Leallyn B. Clapp, Brown University, Providence, Rhode Island
James V. DeRose, Chester High School, Chester, Pennsylvania
Robert K. Fitzgerel, Ohio Wesleyan University, Delaware, Ohio
Edward C. Fuller, Beloit College, Beloit, Wisconsin
Eric S. Graham, Kenyon College, Gambier, Ohio
Arthur H. Livermore, Reed College, Portland, Oregon
Richard L. Miller, Los Angeles High School, Los Angeles, California
H. A. Neidig, Lebanon Valley College, Annville, Pennsylvania
Henrietta A. Parker, Shortridge High School, Indianapolis, Indiana
Robert J. Shewbert, Grant High School, Portland, Oregon
Laurence E. Strong, Earlham College, Richmond, Indiana
Wendell H. Taylor, The Lawrenceville School, Lawrenceville, New Jersey
Frank H. Verhoek, The Ohio State University, Columbus, Ohio
Paul H. M. Westmeyer, University High School, Urbana, Illinois
Harold V. Wik, Sunset High School, Beaverton, Oregon

[4] Sanderson, R. T., "Principles and Construction of New Chemistry Teaching Aids," Bureau of Audio-Visual Instruction, State University of Iowa, Iowa City, Iowa, 1959.

College. The two colleges are included as the result of the belief which developed among the conference participants that the new course is essentially an introduction to chemistry and is not limited to high school use alone.

A major objective of the first year of trial is to determine the effectiveness of the course materials developed for introducing chemistry to students. It is planned to produce a revised text and laboratory guide as a result of this experience. To evaluate the new course and to aid the teachers, a program of school visitations and correspondence is being undertaken. A conference of the teachers and staff is planned during the winter and a second conference at the conclusion of the school year.

The trial year is being directed by Laurence E. Strong, Arthur H. Livermore, H. A. Neidig, and M. Kent Wilson. Leallyn B. Clapp is handling a large part of the editorial work. *Chemical Bond Approach Project* is the name selected for the trial program, and the new course is being referred to as CBA Chemistry.

Three institutes will be held during the summer of 1960 for teachers interested in studying the CBA chemistry course. Brown University, Kenyon College, and Reed College will each have one of these institutes with financial support provided by the National Science Foundation.

A grant of $228,550 has been made to Earlham College by the National Science Foundation. This will support an expanded trial of CBA chemistry in about 50 high schools.

Headquarters for the project is at Earlham College, Richmond, Indiana. Those interested in seeing materials developed or interested in participating in the trial program should get in touch with Laurence E. Strong.

The authors of this report and the participants in the writing conferences are much indebted to the Crown-Zellerbach Foundation for its initial support, and to the National Science Foundation for its continuing support.

Irving S. Bengelsdorf[1]
General Electric Research Laboratory[2]
Schenectady, New York

Teaching Scientific Russian:

An experiment in educational television

In recent years, the realization of the quantitative and qualitative growth of the Soviet effort in all fields of scientific endeavor created some interest among American scientists to learn to read Russian. This interest led several of my scientific colleagues at the General Electric Research Laboratory to request a course in the fundamentals of reading Russian scientific articles. In answer to this request, I presented, in the spring of 1957, a basic linguistic introduction to the Soviet scientific literature to a class of 25 General Electric scientists. The group met for two hours, one night a week, over a twelve-week period. These lectures were quite successful, and when it ended, I received further requests from other scientists to repeat the course in the autumn. This could not be complied with because of other commitments to the end of the year.

On October 4, 1957, the Soviet Union launched Sputnik I; this single technological feat served as the "straw which broke the camel's back" with respect to the attitude of Western science towards the Soviet scientific effort. Overnight, the interest in the study of Scientific Russian became compelling. Arrangements were made with the Adult Education Division of the Schenectady Public School system to teach the above-described course in the evening in a Schenectady high school. Two days after its announcement, limited to scientific establishments in Schenectady, the class had its enrolled quota of 30 and a waiting list of 65 applicants. Requests were received from scientists in Albany and other areas outside of Schenectady to present classes there. This was not possible; it then occurred to me that these scientists in "outlying areas" could best be accommodated by a course in Scientific Russian via television.

To implement this idea the members of the Education Committee of the Eastern New York Section of the American Chemical Society were consulted. They, in turn, approached the Mohawk–Hudson Council on Educational Television (MHCET) and WRGB-TV, the General Electric television station in Schenectady. Both agreed to telecast the proposed language programs.

Presented before the Division of Chemical Literature at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959.

[1] The author studied Scientific Russian with Professor J. G. Tolpin at the University of Chicago during the 1948–49 academic year. Following this training he regularly read the Soviet scientific journals and published translations of Soviet articles, e.g., "The Present-Day State of the Theory of Chemical Structure," J. CHEM. EDUC., 29, 2–14 (1952). He early became aware of the impressive progress of Soviet science, and in a series of lectures (*Science Service News Release*, October 28, 1953) stated that the increasing eminence and future development of Soviet science make it imperative that well-informed scientists keep abreast of scientific developments in the U.S.S.R. At that time, he advocated that a reading knowledge of Russian should be required in studies leading to doctorate degrees in scientific fields.

[2] Present address: TEXUS Research Center, Texas-U. S. Chemical Company, Parsippany, N. J.

How long should the course be? As the undertaking was experimental in nature it was decided to present an abbreviated version of the course during two one-half hour programs each week (Tuesday and Thursday) for a period of 12 weeks running from February 4 to April 24, 1958. At what time of day should the one-half hour lesson be presented? Because of the normal commercial operating schedule of WRGB, and the daily schedules of the intended viewers, the only possible program time was either 1:30 or 6:30 A.M. We chose the latter time with misgivings; the only consolation was that a 6:30 A.M. "Sunrise Semester" television course in literature in New York City had been quite successful. But, of course, one couldn't extrapolate the experiences of a literature program in New York City to a Russian course in the Tri-City area of Albany, Schenectady, and Troy, New York.

Due to time required for program announcements, introductions, etc., the 24 one-half hours of telecasting actually represented considerably less than half of the teaching time devoted to the classroom course. The contents of the course, therefore, were changed to accommodate this decrease in instruction time.

Course Content

Each program opened at 6:30 A.M. with the greeting Good Morning (Доброе Утро), and a short topic such as:

An event of current interest:
The new Soviet ambassador is Mikhail A. Men'shikov.
(Новый советский посол—Михаил А. Меньшиков.)
An expression of time:
winter (зима) spring (весна)
summer (лето) autumn (осень)
A Russian proverb:
Time is money. (Время—деньги.)

The above was done to oblige the unexpected number of non-scientifically trained viewers who were following the programs.

The next few minutes were devoted to an announcement by MHCET which identified the program. This was followed by the main body of the lecture.

The first topic of instruction was the consideration of the 33 Cyrillic characters of the Russian alphabet. It was explained that although the strange alphabet was an initial psychological block to the study of Russian, that it was relatively easy to learn. One could then progress to the study of vocabulary.

Vocabulary

Complete cognates:		
appetite		radioactive
аппетит		радиоактивный
Half-cognates:		
Pacific Ocean	gamma-ray	infrared
Тихий Океан	гамма-луч	инфракрасный
Non-cognates:		
red	star	horsepower
красная	звезда	лошадиная сила

The first group of words studied were complete cognates to English or to German, French, or Spanish—languages which are familiar to scientists in this country. Thus, "appetite" is borrowed from the French, while "radioactive" is from the English. The half-cognates consist of words of both Russian and non-Russian origin. One finds this same construction in German as well as in Russian, e.g., the Pacific Ocean (Das Stille Meer), gamma-ray (gamma-strahl), and infrared (infrarot). The transition was then made to non-cognates or words of only Russian origin. The adjective "red" and the noun "star" form a phrase which not only describes one of the symbols of the U.S.S.R. but is also the name of the journal published by the Soviet army. The word for horsepower is the literal translation of the English or the German (Pferdestärke).

horse = pferde = лошадь
power = stärke = сила

The study of Russian grammar was begun by illustrating the two simple rules that (*a*) there are no definite or indefinite articles in Russian, and (*b*) there is no simple present tense of the verb "to be"—words like "is" or "are." The two following sentences demonstrate these rules.

(The) book (is) on (the) table.
Книга на столе.
Silver (is a) metal, but steel (is an) alloy.
Серебро—металл, а сталь—сплав.

Grammar study was then developed to include the declensions of nouns and adjectives, adverbs, and the conjugation of verbs. Particular attention was paid to the participles since these verb forms occur quite frequently in the technical and scientific literature. Examples of sentences were provided to illustrate the presentations. Unfortunately, the short time allotted to the program series only permitted a superficial look at the problems of syntax.

Source materials for the TV presentation were as follows:

Scientific journals: Those issued by the Academy of Sciences of the Soviet Union were shown and described and the student viewers were told to consult them, particularly *Doklady* (Доклады—Reports of the Academy of Sciences) for it contains the most recent and diverse research reports in a condensed fashion.

Newspapers: Pravda (Правда) of the U.S.S.R. and *Novoe Russkoe Slovo* (Новое Русское Слово) of New York City were employed from time to time to emphasize a teaching point.

Postage stamps: The Soviets issued a large number of stamps last year especially dealing with the International Geophysical Year. The latter in Russian is Международный Геофизический Год; the Russian abbreviation, therefore, is МГГ instead of IGY.

Textbook: "Teach Yourself Russian" by Prof. M. Fourman of the University of Kiev (David McKay Company, Inc., New York) was selected because it is well written, adapted for home-study, concise, and was attractively priced at $2.50.

Guide sheets: These personally prepared guide sheets were an outline of the television presentations and a catalogue of the various grammatical declensions and conjugations which were considered.

Each program was concluded with the farewell greeting "Until we meet again" (До свидания) and an indication to tune in next Tuesday (Вторник) or Thursday (Четверг).

Listener Response

The Tri-City area's response to this language series was a series of surprises. The first surprise occurred when the first section of the guide sheets was announced for free distribution. The expectation had been for about 250 scientists to view the program in the area. On this basis, the Eastern New York Section of the American Chemical Society had agreed to pay for the incurred postage costs. Instead, WRGB and MHCET

were deluged with over 4500 requests for the sheets and about 1000 requests for books. The MHCET assumed the extra postage burden and also had to hire additional clerical help to process the requests.

In addition, the publishers, in pre-program correspondence, had indicated an adequate supply of textbooks. This was sold out the first week of the telecasts; a new printing had to be ordered which, unfortunately, did not arrive until the sixth week of the course.

Due to the unexpected demand, the concluding section of the guide sheets was not completed until the tenth week. In spite of this late availability of the sheets, and a price of ten cents to cover mailing costs, about 1000 requests were received for them.

The final surprise came when the student-viewers were invited to attend the last telecast of the series. Approximately 90 people arrived, some from as far away as Glens Falls, New York, and Pittsfield, Massachusetts. They obviously had begun to drive about 4:30 A.M. to arrive at the WRGB studios at 6:00 A.M.

What did this language-program series accomplish? The achievements of the program series were several:

The primary purpose of the course, the transmission of knowledge of the Russian language, was achieved. The students are no longer fearful of the Russian alphabet; many can translate title headings of articles; and a few have written that they actually are able to translate with the aid of a dictionary. Many viewers had their taste for the Russian language whetted and are continuing its study elsewhere.

The community was made aware of the country's language deficiencies, not only in Russian, but even in the more common languages as well. Subsequent to the course, numerous classes in the study of the Russian language sprang up throughout the area; the Schenectady area today is undoubtedly one of the better-versed areas in the nation with regard to knowledge of the Russian language.

The surprising positive response from the WRGB area viewers clearly showed that a potential for educational television programs did exist in the Tri-City area—even though it is not a large metropolitan center. Since the area does not have an educational television station as yet, educational programs must use commercial telecasting channels and time. The Scientific Russian program, because of the time of the broadcast, was the first to reach a large audience of male viewers.

The early morning viewing time of 6:30 A.M. was acceptable in spite of pre-program misgivings. Numerous viewers indicated that they were relatively free and unbothered at that time. There is no doubt, however, that an evening viewing time would be even more suitable for both students and instructor.

The success of the program paved the way for similar telecasts of the non-scientific aspects of the Russian language throughout the country.

The amazing response of children to the telecasts was personally gratifying. Of the large number of high school viewers one wrote that he wanted to enter a science contest with an exhibit dealing with the phenomenon of Liesegang rings, but the only pertinent reference he could find was published in *Colloid Journal* (Коллоидный Журнал). After viewing the telecasts, and armed with a dictionary, he painstakingly translated the paper word by word to obtain the needed information.

Several six- and seven-year-old viewers made copies of the Russian alphabet and showed them to their classmates. This bears upon the suggestion that the proper time to begin foreign language instruction is at the elementary school level. The future university student, well-trained in language before he enters undergraduate training, will have the time which is ordinarily devoted to language instruction, to obtain knowledge in his or her specialization.

Acknowledgments

The author wishes to thank Dr. Leonard Niedrach of the Eastern New York Section of the American Chemical Society, Mr. Donald Schein of MHCET, Mr. Albert Zink and Mr. Caleb Paine of WRGB-TV, and the General Electric Company, for making the Scientific Russian telecasts possible.

NSF Summer Conferences for College Chemistry Teachers

The NSF is sponsoring summer (1960) conferences on chemistry and chemical engineering topics. Participants will be chosen by the conference directors and their staffs. Inquiries and requests for application blanks must be addressed to the directors listed below. Most deadlines for applications will be early in April.

BUTLER UNIVERSITY, June 19–July 2: *Recent Developments in Non-Aqueous Solvents.*
Ralph K. Birdwhistell, Dept. of Chem., Butler Univ., Indianapolis 7, Ind.

CORNELL COLLEGE, June 13–24: *Radioisotopes and Their Uses.*
Cecil F. Dam, Physics Dept., Cornell College, Mt. Vernon, Iowa.

UNIVERSITY OF FLORIDA, June 7–18: *Nuclear Resonance.*
Wallace S. Brey, Jr., Dept. of Chem., University of Florida, Gainesville.

PURDUE UNIVERSITY, July 11–23: *Chromotgraphy: Theory and Practice.*
Warren W. Brandt, Dept. of Chem., Purdue University, Lafayette, Ind.

TUFTS UNIVERSITY, July 12–22: *Recent Advances in Chemical Bonding.*
M. Kent Wilson, Dept. of Chem., Tufts University, Medford 55, Mass.

WASHINGTON UNIVERSITY, June 7–30: *Systems Engineering Theory for Chem. Eng. Teachers.*
Gerald L. Esterson, Dept. of Chem. Eng., Washington University, St. Louis 30, Mo.

Samuel A. Goldblith
Massachusetts Institute of Technology
Cambridge 39, Massachusetts

The Teaching of Food Technology at Massachusetts Institute of Technology

Food technology has been defined as the application of science and engineering to the production, preparation, processing, packaging, distribution, and utilization of foods. It is a relatively new field of scientific endeavor, and one of which most high school students are not aware. Its curriculum at any institution is influenced markedly by the factors of heredity and environment. The factor of heredity is inherent in the professors in the department and particularly in the department head. The factor of environment deals with the location of the department within a given school, e.g., within the School of Agriculture or at the School of Science.

Until 1945, food technology at MIT was taught within the department of biology as the "Industrial Biology Option." Thus in the years between 1927 and 1944 the program was considerably influenced by the environmental factor and was heavily weighted in the areas of the biological sciences, particularly bacteriology, biology of food supplies, chemistry of water and sewage, chemistry of foods, comparative anatomy, general biology, industrial microbiology, and industrial hygiene.

This curriculum also emphasized the classical biological sciences of zoology, anatomy, physiology, and theoretical biology. In addition it offered several courses in various aspects of chemistry, a brief course in food engineering, two courses in the technology of food supplies (that is, the raw materials), and two courses in food processing or the technology of food products. In the senior year, a thesis was required dealing with a small research investigation conducted by the student. A further point of interest in this curriculum is the so-called "general study" required in the second, third, and fourth years. This general study dealt with non-professional subjects such as philosophy and history.

In 1944 the Administration and Corporation of MIT recognizing the importance of the food industry and the necessity for training food technologists to enter this industry, created as a separate department on a par with other departments, the department of food technology within the School of Science. The change resulted in an environmental effect upon the teaching and research in the department. The choice of Chairman, Professor Bernard E. Proctor, recently deceased, has had a marked hereditary influence on the department at MIT and, in fact, in food technology teaching all over the world.

By 1949 the department recognized the need for the proper teaching of thermodynamics and unit operations in food technology. Instruction in this area was initiated within the department by the appointment of a chemical engineer who had had considerable experience with foods and who used food materials and food equipment for problem examples. The instruction in thermodynamics was coordinated with the course in food engineering given by the mechanical engineering department.

In 1949 a committee was appointed by the president to report to the faculty relative to the general educational policies of the Institute. This committee was known as the Lewis Committee, named after the chairman, Dr. Warren K. Lewis, famed emeritus professor in the department of chemical engineering.

The report of this committee strongly recommended that (1) there should be an increase in the number of subjects taught in the humanities and social sciences, and (2) that it be made compulsory for every student to take courses in the humanities and social sciences for at least eight semesters. The committee further recommended the adoption of an integrated program in the humanities and social sciences. As a result, a revised program of instruction in all courses with the Institute evolved. As applied to the department of food technology this varies markedly from the original program offered in 1934. In certain respects, the present program differs even from that existing in January, 1958.

Organic chemistry will be moved from the third to the second year, qualitative analysis will be removed from the curriculum, and quantitative analysis will be taught in the third year after the student has acquired a basic knowledge of physical chemistry. Thus quantitative analysis and related laboratory work may be taught at a more advanced level. In addition, this program will raise the level of teaching in the department. Courses formerly offered in the senior and junior years will be offered in the junior and sophomore years,

Presented before a joint meeting of the New England Association of Chemistry Teachers and the New England Biological Association, December 5, 1959, at the Massachusetts Institute of Technology.

Contribution No. 395 from Department of Food Technology, MIT.

respectively. This will allow more time for elective subjects in the senior year, when students are better able to take such elective training and utilize it to best advantage.

Furthermore, this new curriculum will offer an extra course in food bacteriology to teach newer techniques in the quantitative aspects of bacteriology as applied to foods, a stronger course in the chemistry of nutrition, and a stronger course in the applications of chemical engineering in food technology, with an extra laboratory section. Mathematics is required for four semesters beginning with differential calculus, and physics is taught at a corresponding level. Typical elective subjects that are to be offered are Industrial Microbiology, Bacteriology of Foods, Food Applications of Ionizing Radiations, New Food Product Evaluation, and Introduction to Industrial Management.

In the teaching of food technology per se, the subject matter should deal with the fundamental disciplines of microbiology, mathematics, chemistry, physics, and the like, and the applications of these techniques to the processing of foods integrated and expressed through an engineering operation. At MIT this is not taught by means of descriptive courses concerning the main food industries and the principal food products such as dairy products, cereals, fruits, and vegetables, but rather by a positive method dealing with the sequence of unit operations common to all food industries; food commodities are used only as examples.

Present-day emphasis on some phases of science and engineering has distorted to a disproportionate extent the relative importance of military instruments, while the tremendous relative survival value of food, and the role of food technologists in their functions to humanity is practically forgotten. The absence of only a half-dozen well-balanced meals could certainly make an indelible impression on our population of the primary role which the many million persons in the food industry play in our modern civilization. The teaching of food technology presents just as great a challenge as the training of the youth who may tomorrow man the rockets, build the electronic mechanisms which visit the moon, or penetrate the depths of the universe.

LETTERS

To the Editor:

Congratulations are due James M. Thoburn for his technique and presentation of weight titrations (J. CHEM. EDUC., **36,** 616 (1959)). The method should find many applications.

In the most accurate work it should be emphasized that correction must be made for the effect of buoyancy of air on the solution delivered. Under usual conditions this correction amounts to slightly more than one part per thousand of the weight for solutions with a density of about one.

The buoyancy equation (see rt. col.) requires an approximate knowledge of the density of the solution (within ± per cent for an accuracy of one part in 10,000). Most dilute aqueous solutions have a density equal to one within this tolerance, so that a common correction factor may be applied to all sample weights. One part in 10 accuracy in the factor is sufficient if the solution density is not greatly less than one. For solutions of other densities, the correction factor must be calculated for the particular case.

Alternately the correction may be determined from the approximate volume of solution delivered as indicated by the syringe graduations. This method has particular advantage for solutions of unknown density.

When considerable work is done with several concentrations of a solution, it is convenient to plot the correction factor as a function of weight per cent (or molelity) of solute. These curves are approximately linear and provide quick access to the factor for a solution of any approximate concentration.

$$\delta = fw;\ f = 1.2 \times 10^{-3}((1/d) - (1/8.4))$$
$$\delta = 1.2 \times 10^{-3}(V - (w/8.4))$$

w = weight in air of solution
δ = buoyancy correction (add to w)
f = buoyancy correction factor
d = density of solution
V = volume of solution

ALAN SYVERUD

UNIVERSITY OF KANSAS
LAWRENCE, KANSAS

EDITOR'S NOTE: Dr. Thoburn adds his endorsement to the above comments. He points to the article by P. K. Faure and J. A. Gledhill (*Anal. Chem.*, **30,** 1304 (1958)) as a useful reference.

Chem Ed

BOOK REVIEWS

The Sequestration of Metals

Robert L. Smith. The Macmillan Co., New York, 1959. vii + 256 pp. Figs. and tables. 16.5 × 25.5 cm. $8.50.

Organic Sequestering Agents

Stanley Chaberek, the Dow Chemical Co., and *Arthur E. Martell,* Clark University. John Wiley & Sons, Inc., New York, 1959. xv + 616 pp. Figs. and tables. 16 × 23.5 cm. $25.

In microscopy, two objectives are needed, a low-power lens to scan a large field and to define major points of interest, and a high-power lens to resolve the underlying nature of these points. By analogy, the two works under review involve these two objectives in their respective considerations of sequestering agents.

Dr. Smith delineates the "theoretical considerations and practical applications" of "the sequestions of metals." His book is addressed to the graduate chemist "to whom sequestering agents . . . could be a useful tool rather than a prime study." The work is highly readable, employs simple explanations of coordination phenomena where possible, uses a minimum of mathematical formulas, and offers well-selected and well-presented bibliographies following each section.

Drs. Chaberek and Martell scrutinize most minutely "the chemical behavior and applications of metal chelate compounds in aqueous systems." Their monograph will be of profound importance to researchers in many fields of science and technology. Martell and Calvin in "Chemistry of Metal Chelate Compounds" (Prentice-Hall, 1952) carried this field of knowledge through the 1940's and brought into focus for many workers new areas of research challenge. The monograph by Chaberek and Martell is a noble successor to that work and reflects the advance of both the theory and application of water-soluble chelates into the late 1950's. The authors are to be commended on the frequent use of structural formulas, informative graphs, summary tables, and the extensive coverage of the literature. They also may be congratulated for their thorough and yet concise consideration of metal buffers, that is, the regulation of "free" metal ion concentration by the use of complexing agents. The principle of the metal buffer underlies most applications for sequestering agents.

Smith defines sequestration as "the suppression of a particular property or properties of a metal in solution, without the removal of that metal either into another phase nor its concentration into a . . . portion of the original phase [as in ion exchange], while at the same time the agent used for the purpose of this sequestration must not introduce any new factor . . . which makes the system unsuitable for the original purpose." He states further that the agent used in the sequestration, so defined, "always acts by forming coordination compounds of the metal and are most frequently chelating agents." However, to this reviewer, Dr. Smith's definition of sequestration appears too broad and might even be held to encompass the use of oxidation or reduction reactions to suppress particular properties of a metal.

Chaberek and Martell first define sequestering agents as "complexing reagents which form stable, but soluble, complexes of metal ions," but later state "when a ligand forms a stable, water-soluble metal-chelate, the ligand is said to be a sequestering agent, and the metal is said to be sequestered." This latter definition would rule out unidentate ligands (e.g., halo, cyano, thio, hydroxo) as sequestering agents and to confine sequestration to aqueous systems.

It is of interest to compare the relative page space allotted to various topics by Smith and by Chaberek and Martell, respectively: Table of contents and indexes, 5 and 6%; theory and properties, 45 and 48%; analytical chemistry, 10 and 13%; agriculture and biological sciences, 11 and 14%; commercial applications, 29 and 19%. In interpreting the last percentage, it should be noted that Chaberek and Martell summarize many commercial applications in a 12-page, classified table.

Both works give extended consideration to the aminopolycarboxylate reagents including ethylenediaminetetraacetic acid (EDTA); the introduction of such compounds constitutes the salient advance in sequestering agents during the past 20 years. Both monographs are highly recommended by the reviewer to chemists and allied technologists as basic reference works on sequestration—a phenomenon of major importance for contemporary chemistry, chemical technology, diverse industries, agriculture, and the biological sciences.

A. J. Barnard, Jr.
J. T. Baker Chemical Co.
Phillipsburg, New Jersey

Semimicro Experiments in General Chemistry and Qualitative Analysis

Nicholas D. Cheronis, Brooklyn College, and *Herman Stein,* Bronx Community College. John De Graff, Inc., New York, 1958. x + 310 pp. Figs. and tables. 19.5 × 26 cm. Paperbound. $4.

A new approach to teaching a laboratory course in freshman chemistry is offered by Cheronis and Stein. The introduction of semimicro techniques into the first year course in chemistry, as proposed by these authors, should add a great deal to the stature of the freshman chemistry laboratory course. Students using this manual will be required to exercise more care in performing experiments. This approach enables schools to handle larger enrollments much more efficiently, with considerably less hazard.

Some noteworthy features of the manual are the use of microscope techniques and organic reagents. The experiments on Boyles' and Charles' laws are especially well designed. Here, the qualitative analytical scheme employs micro-techniques with optional spot testing using organic reagents.

The extreme detail of the laboratory procedures and the nature of the questions following each experiment may, however, hinder the exercise of original thought by

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Sidney Siggia, Continuous Analysis of Chemical Process Systems
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J. S. Rowlinson, Liquids and Liquid Mixtures

the student. There is a section devoted to organic chemistry that requires specialized equipment that may not be available to schools with limited budgets.

The use of this manual should increase the caliber of work performed by the first year student in freshman chemistry.

THEODORE R. WILLIAMS,
College of Wooster
Wooster, Ohio

Continuous Analysis of Chemical Process Systems

Sidney Siggia, Olin Mathieson Chemical Corp. John Wiley & Sons, Inc., New York, 1959. xiii + 381 pp. 113 figs., 11 tables. 15.5 × 23.5 cm. $8.50.

This volume presents a compilation of information on most of the current instruments suitable for the continuous analysis of process streams. With few exceptions, as the author points out, the material presented was taken from technical bulletins of instrument companies. After two very brief introductory chapters, the remaining chapters are titled according to a physical constant, a technique, or the substance being measured. Included in the first category are refractive index, density, viscosity, and electrical constants. Techniques include infrared, ultraviolet and visible absorption, coulometry, x-ray fluorescence, vapor chromatography (the term "gas chromatography" is now recommended), mass spectrometry, and automatic chemical analysis. Separate chapters discuss gas analysis and the determination of water, oxygen, carbon dioxide, and combustibles. A very short final chapter is included on "Instruments in the Research or Development Stage" at the time the manuscript was prepared. Only brief mention is made of waste stream analysis, a part of chemical process systems; waste gas analysis is of particular importance relative to air pollution. Several companies, e.g., Harold Kruger Co. in California, manufacture analyzers for this purpose.

The title of the book and some of the publisher's advertising materials are somewhat misleading. Little is given on principles and desirable background information. A most critical and often difficult problem in continuous analysis is that of sampling. Discussion of this subject would have been of considerable value to the reader.

The book will be helpful to chemists and engineers desiring information on currently available instruments. Students will be appraised of techniques on which most continuous analyzers are based. Items are arranged conveniently and diagrams often help in illustrating design problems in moving from batch to continuous analysis. In most cases examples are given of applications. These portions could well have been expanded to provide the reader with more insight on how the instruments have been used.

Unfortunately, in a book of this type much information already is outdated because of rapid developments in manufacturer's equipment. Thus, instruments such as the time-of-flight mass and nuclear magnetic resonance spectrometers have found several applications in industry. The CEC Model 620 mass spectrometer was not mentioned. The reader must bear in mind, therefore, that improved or new instruments might well be available when the need arises.

This volume presents a description of commercial instruments, together with operating characteristics, in a convenient, compact form. It will be a handy reference book for those desiring information on types of tools available for continuous analysis.

J. MITCHELL, JR.
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

Thermodynamics and Statistical Thermodynamics

John Geldart Aston and *James John Fritz*, both of the Pennsylvania State University. John Wiley & Sons, Inc., New York, 1959. ix + 556 pp. Tables. 16 × 23.5 cm. $8.25.

This book can be considered in two parts.

The first part, comprising about one-half of the book, devotes fifteen chapters to the subject matter of classical thermodynamics. Conventional topics such as First Law, Second Law, equilibria, fugacity, partial molal quantities, solutions of electrolytes and non-electrolytes, electromotive force of cells, systematic calculation of thermodynamic properties in chemical reactions (including use of Third Law data) are covered. In addition, such topics as the generalized thermodynamics of Gibbs; variables other than pressure, temperature, and concentration; and construction and the use of entropy diagrams of gases are presented.

The second part, which contains the remaining eight chapters, is a presentation of statistical thermodynamics. Introductory chapters deal thoroughly with energy levels of particles, atoms, and molecules, and the distribution laws. Molecular distribution functions are then developed and applied to the calculation of the thermodynamic properties of diatomic gases, polyatomic gases, and crystals. The subject is completed with a chapter on the magnetic contribution to thermodynamic properties and a final chapter concerned with the more elegant procedures as represented in canonical and grand canonical ensembles.

The book has a rather extensive group of appendixes which contain, for the most part, supplementary information useful for the statistical calculation of the thermodynamic properties of gases. The results for a number of simple gases are also included.

The presentation and discussion of subject matter is excellent. The authors have tacitly accepted the fact that no text on thermodynamics can be effective without practice with suitable exercises on the part of the student. Consequently, some 400 problems (about one-third derivations and the remainder numerical) appear, not at the end of each chapter, but in the body of the text at the point where the related subject matter is being presented. Thus, the problems serve the purpose of simultaneously developing and crystallizing the ideas in the text.

For those interested in the use of the book as a course textbook in classical thermodynamics, the nice balance in the first part between an excellent presentation of subject matter and worthwhile problems results in as fine a treatment as is to be found anywhere. The level and quantity of material would probably require a semester for coverage by graduate or superior senior undergraduate students in chemistry.

The second part of the book is largely devoted to the statistical thermodynamics relating to non-interacting molecules of diatomic and polyatomic gases. The text and problems dealing with this phase of statistical thermodynamics are excellent. However, because the scope of the subject matter is somewhat restricted, some may find it necessary to supplement the material with other topics not covered in the text.

E. L. PACE
Western Reserve University
Cleveland, Ohio

The Evaluation of Drug Toxicity

Edited by *A. L. Walpole* and *A. Spinks*. Published in London by J. & A. Churchill, Ltd. Little, Brown and Company, Boston, 1958. xi + 138 pp. 58 figs. 16 × 24 cm. $5.50.

This is an interesting book dealing with a very complex subject—drug toxicity. It consists of a series of presentations at the symposium on "The Evaluation of Drug Toxicity" by persons interested in a particular aspect of the over-all picture. The book is relatively short, 128 pages, including references and a brief discussion following each presentation. In addition, a 10-page index is also included, yielding a total of 138 pages. The text material is freely illustrated with photographs, figures, tables and formulae.

Each contributor adds to the over-all picture of drug development, from its synthesis or isolation to the determination of "predictable" toxicity and attempts to uncover "unpredictable" toxicities. The articles and discussions repeatedly emphasize the need for much more knowledge than we presently possess, so that some day we may be able to predict the currently "unpredictable" reactions. It is pointed out that we do have certain pieces of the puzzle, and that current and future research may add to this knowledge so that some day, maybe, the picture will be completed.

The articles are not presented on a level that would be suitable for the beginning student. However, for the more advanced student in the medical sciences and for the physician or researcher interested in drug action and toxicology, the principles set forth or re-emphasized should yield some basis for understanding why

unpredictable reactions may occur, why it is not possible to determine with certainty all adverse actions of a drug using experimental animals or even during limited clinical trials, why some persons may take a drug without any adverse effects while others cannot. The book does not give, nor does it pretend to give, the complete answer to drug reactions. After reading this book one will not be able to point to a person or animal at random and say whether or not he would be affected by the unpredictable reactions, but at least he should have some understanding of a portion of the underlying problems involved. Thus, for graduate students in pharmacology, toxicology, biochemistry, and related fields, it may stimulate thought and eventual solution to some of the problems involved.

W. Homer Lawrence
College of Pharmacy
University of Houston
Houston, Texas

Synthetic Methods of Organic Chemistry. Volume 13

W. Theilheimer. S. Karger, Interscience Publishers, Inc., New York, 1959. xvi + 600 pp. 16.5 × 23.5 cm. $27.50.

The purpose of this series is to provide annually a handy reference for "new methods of synthesis of organic compounds, improvements of known methods, and also old proved methods scattered in periodicals." It is the reviewer's opinion that the author succeeds in his purpose in this volume and even more so when the set is considered as a whole.

In the present volume, 917 monographs are given in 441 pages. This is followed by 159 pages of indexes. The monographs, generally too brief to be followed precisely in the laboratory, are sufficient for evaluation of the cited method by a trained chemist. The monographs are indexed uniquely according to a "simple" system created by the author. Volume 2 of the series discusses this system of classification and the reader should become familiar with it if he is to use the series to the fullest advantage. Further aids are frequent cross-references to earlier volumes.

Beginning in Volume 8, the author has included a section called trends in synthetic organic chemistry. This is fairly valuable since the author has a flair for selecting promising reactions from among the many which are continually disclosed.

The text is surprisingly free from errors. There are a few. On page xi, "*beta*-dimethylacrolein" is given instead of "*beta*-dimethylaminoacrolein." The trends section discusses the use of triaryltin hydrides for the removal of aromatic halogen, but there is no monograph on this in the text.

Practicing organic chemists will find the book a welcome way to get a quick glimpse of recently published synthetic procedures. The reviewer spent a profitable number of hours browsing in the book, for which this book is highly recommended.

Ernest I. Becker
Polytechnic Institute of Brooklyn
Brooklyn 1, New York

Organic Chemistry. A Brief Course

Ray Q. Brewster and *William E. McEwen*, both of The University of Kansas. 2nd ed. Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1959. xii + 401 pp. 25 figs., 31 tables. 16 × 23.5 cm. $7.50.

Although the general aim of the first edition is maintained in this revision, the authors state in the preface, "we have rewritten and rearranged the material almost completely—in such a way that the properties of aliphatic and aromatic compounds are presented in an integrated manner." Furthermore, after an introductory chapter on atomic structure, bonds, etc., the authors introduce their subject with a brief treatment of methyl and ethyl alcohols. The usual order of presentation of topics (with a few exceptions) is then presented from the standpoint of integrated subject matter.

More stress is given to reaction mechanisms, although "the theoretical material is introduced in a gradual manner." Thus, we find in a text which is designed for one semester (or two quarters), the gamut of unique modes of presentation of organic chemistry—integrated subject matter, inverted topic order, reaction mechanisms, electronic theory, and some consideration of atomic and molecular orbitals.

This text covers 21 chapters (plus a foreword) in a total of 401 pages. Its size is almost the same as that of the first edition. Each chapter includes a group of excellent review questions, the answers for which are presented at the end of the book. A novel and valuable addition is the inclusion of the picture of a famous organic chemist at the beginning of each chapter, plus a biographical sketch in a footnote.

This text is well written, with clarity of expression and emphasis on fundamental processes. It is attractively bound and is remarkably free from errors. This reviewer feels that it is a demanding text for a one-semester course, especially in its inclusion of topics and mechanisms normally found in a more comprehensive treatment. This argument is countered somewhat by the freedom of choice of topics by the individual teacher. Some teachers may find the presentation of fats and oils, and of proteins, too brief for the needs of the groups for which it was written.

Roy G. Bossert
Ohio Wesleyan University
Delaware, Ohio

High Polymers. Volume 12: Analytical Chemistry of Polymers. Part 1

Edited by *Gordon M. Kline*, National Bureau of Standards, Washington, D. C. Interscience Publishers, Inc., New York, 1959. xviii + 666 pp. Many figs. and tables. 16 × 23.5 cm. $16.50.

The latest in the Interscience High Polymers series consists of twenty chapters written by various industrial chemists concerning analytical aspects of a wide variety of commercially important polymers. The chapters average about thirty pages, and some of the topics are: Acrylic Plastics, Alkyds, Cellulose Derivatives, Epoxy Resins, Ethylene and Fluoroethylene Polymers, Phenolic Resins, Polyamides, Polyesters, Rubbers, Plasticizers, and Drying Oils.

The format is good, and the book is generally free of typographical errors.

This book will be of most value to industrial chemists who are engaged in the manufacture of some of the better known monomers and polymers. A number of analytical procedures are given which have been worked out by the various companies and which have not been published before. The unpublished procedures are usually described in great detail and a large number of references to published procedures are given.

Most chapters begin with a discussion of quality control of the monomers involved including, in addition to methods for direct assay of monomers, such topics as moisture determination, residue, density, refractive index, and determination of contaminants such as heavy metals. It is somewhat surprising to find that very little is said concerning the use of vapor phase chromatography in the analysis of liquid monomers. Discussion of the monomer is followed by a presentation of analytical procedures for the polymer including elemental analysis and many other quality control techniques.

This book was not intended to include any exhaustive theoretical discussion of the methods employed. In most chapters one finds only the briefest of introductions. However, the procedures are described in such detail that they could be carried out by people with very little technical training. Part 2 of this volume, which is in preparation, will supposedly cover the theoretical aspects more fully.

J. E. Mulvaney
University of Illinois
Urbana

Polymer Reviews. Volume 2: Linear and Stereoregular Addition Polymers

Norman G. Gaylord, Interchemical Corp., New York, and *Herman F. Mark*, Institute of Polymer Research, Polytechnic Institute of Brooklyn. Interscience Publishers, New York, 1959. x + 571 pp. Many figs. and tables. 16 × 23.5 cm. $17.50.

A book on stereoregular polymerization has been needed because much of the data in this field appears in uncritical patent literature rather than in accessible journal articles. Gaylord and Mark are well qualified, because of their industrial and academic backgrounds, to write this timely critical review covering both the experimental and theoretical aspects of this new segment of polymer science.

Because of the rapid development in this field, the authors had to revise their manuscript as it was being processed. Yet, the book is free of all but a few unimportant errors.

(*Continued on page A252*)